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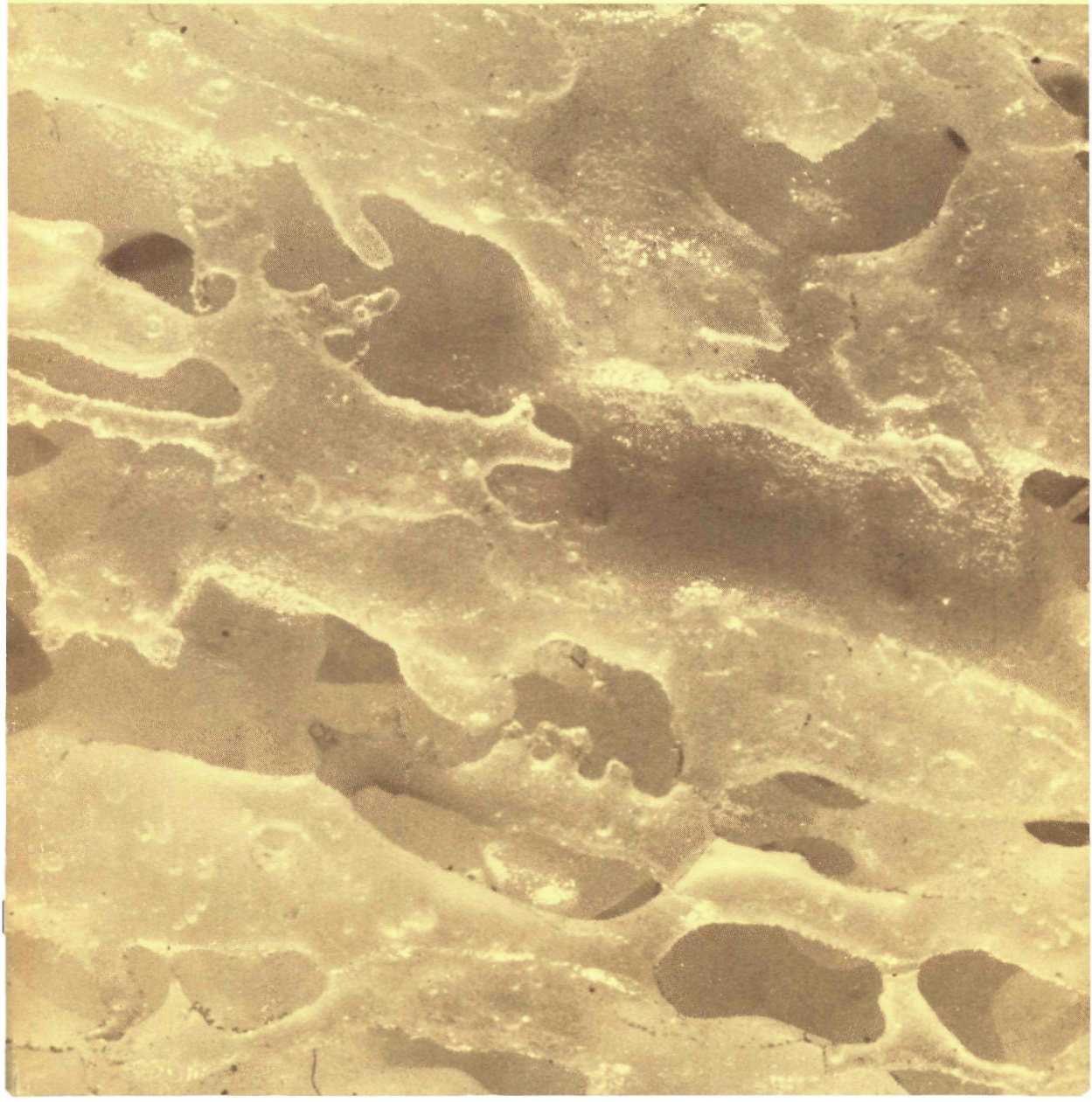
POROUS POLYMETHYLMETHACRYLATE CEMENT

DEVELOPMENT AND EVALUATION OF A POTENTIAL IMPLANT MATERIAL

J. R. DE WIJN



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DEVELOPMENT AND EVALUATION OF A POTENTIAL IMPLANT MATERIAL

J. R. DE WIJN

CURRICULUM VITAE AUCTORIS

18 - 11 - 1941	geboren te Poerwakarta (Ind.).
1953 - 1959	gymnasium β, Rijnlands Lyceum te Wassenaar.
1959 - 1968	studie in de scheikunde, specialisatie technische scheikunde, i.h.b. technische polymeerchemie.
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PROMOTORES:

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DEVELOPMENT AND EVALUATION OF A POTENTIAL IMPLANT MATERIAL

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE
GENEESKUNDE AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN,
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. P. G. A. B. WIJDEVELD
VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN
IN HET OPENBAAR TE VERDEDIGEN OP
DONDERDAG 7 JANUARI 1982 DES NAMIDDAGS TE 4 UUR

DOOR

JOOST ROBERT DE WIJN

GEBOREN TE POERWAKARTA

1982

krips repro meppel

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One of the characteristics of the researcher in biomaterials is his need for a large number of colleagues,coming from many different disciplines, to do his work.
In performing and completing this study, I certainly was in the privileged position to be able to rely on the expertise, skill, cooperation and the good-fellowship of many people.
I gratefully acknowledge their indispensable contributions.
P.J. van Mullem (Dept. of Oral Histology) cooperated extensively in designing the animal experiments and performed the histological evaluations involved in this study. His "biological response" to my materialistic demands has been most favourable.
Without the enthousiasm of R. Feith, J. Ypma, R. Huiskes (Dept. of Orthopaedics), M.M.A. Ramselaar (Dept. of Prosthetic Dentistry) and J.M. Vaandrager (Dept. of Plastic Surgery, University of Rotterdam) to incorporate my ideas in their own research, much of this study would have been confined to theory.
Carrying out the laboratory experiments cannot be a one man's task. I am indebted to P.J.A. van Kesteren (Dept. of Dental Materials) for never refusing me "just another" analysis or preparation and being so devoted during the years of our working together.
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In preparing the manuscript, I could rely on the professional and prompt service of J.L.M. van der Kamp, H.A.W. Bongaarts and H.W.M. Ebben (Dental Photography) for the preparation of so many photographs. J. Konings (Medical Illustration) provided a large part of the drawings.
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For committing this study to paper, I was fortunate enough to have the patient and cheerful assistance of Miss Mariet Strijbos.

CONTENTS

1.1 Scope of the work

Among the numerous materials, including metals, polymers and ceramics, which have become available for substitution or enforcement of lost and disabled parts of the human body, polymethylmethacrylate - or acrylic resin - undoubtedly has the longest history. Although the material has been and is used in a variety of biomedical applications (see section 1.2) the largest volume is "consumed" in the form of in situ curing formulations for dental purposes and as bone cement. In this latter form it is used to anchor joint prostheses to the bone that is being reconstructed and to fill up defects in the skeletal system.
Three concerns always accompanied the use of acrylic resin as bone cement.

1. The polymerization of monomeric methylmethacrylate to polymethylmethacrylate is an exothermic reaction and causes temporarily high temperatures in the rapidly hardening material. How will the tissues, facing the material, react to temperatures sometimes as high as 100° C, albeit for a short time?
2. When the cement, in its still uncured state, is implanted in the body, monomer will contaminate the biological system and after curing, residues of monomer will slowly leak out of the implant for prolonged times. Monomeric methylmethacrylate is toxic, causing cardiac and respiratory functions to fail at sufficiently high concentrations and provokes histological and immunological reactions at much lower concentrations.
3. As there is no adhesion between acrylic cement and surrounding tissues, a mechanical bond between them can only be formed by a process of interlocking which takes place when the still plastic cement flows into interstices and irregularities of the bone. Nevertheless, a close contact between cement and bone is seldom found after prolonged periods and the material is always separated by a connective tissue membrane from the opposing bone. This is not in favour of a mechanically stable fixation so that loosening of the implant often occurs, certainly when forces are exerted on it.

This work describes the development of a modification of cold-curing acrylic cement in which the last mentioned problem of mechanical fixation is solved by creating a sponge-like porosity in the material. Under certain conditions bone can grow into the pores, providing better means for mutual interlocking and thus for enhanced strength of the resulting bond between bone and implant.
The porosity is obtained by dispersing an aqueous gel through the

cement when it is still uncured. After hardening of the cement the aqueous phase diffuses out of the material into the biological environment, leaving pores in it.
It appears that the gel functions as an effective sink for the heat developed during polymerization so that the first mentioned problem of high temperature peaks seems to be alleviated as well.
In the next sections and chapters both background, synthesis, characterization of the material and its biological evaluation will be discussed.

1.2. History of biomedical acrylic resins

During the first three decades of this century the fast developing chemical science provided the basis for our present large choice of high molecular weight materials. From these, polymers of methacrylate esters - particularly polymethylmethacrylate - were among the first to find application as biomaterials.

In the industrial field the material had attracted attention by a combination of properties such as high transparancy, relatively high toughness and strength and easy processability. It was succesfully employed as a substitute for the heavy and vulnerable inorganic glasses in such applications as windscreens for motor vehicles and aeroplanes, lamp glasses, etc.

The same properties, not in the least the outstanding optical qualities, readily caused polymethylmethacrylate to be adopted by the dental profession for the fabrication of full dentures and artificial eyes. In an interesting historical review W. Bauer (1949) claimed to have seen the potential dental application as early as 1930, working at the Röhm and Haas factories in Germany. This company obtained patents for denture fabrication out of polymethylmethacrylate in 1935 and 1937.
In the United Kingdom the ICI company build a methacrylate plant in 1932. The primary goal was the application of the material in safety glass laminates. In 1933 investigations were started to the possible use of the product as denture base material. Two years later, G.B. Drury and coworkers (1935) reported that more than 2000 ICI employees had received a "Kallodent" prosthesis to full satisfaction and promised the release of the material for the dental profession in due time. The U.S.A., where the material had been introduced probably by the American division of Röhm and Haas, saw the first commercial acrylic denture base material in 1937. Kimball (1938) mentioned the material, stating that it was to early to say anything about its qualities.

In 1941 "acrylic resins" had become a main heading in the Index to Dental Literature and the Index Medicus, covering reports on their use as materials for dentures, artificial teeth, inlays, crowns, bridges but also for artificial eyes, noses and ears (Munson and Heron, 1941). Although these external prostheses and devices were not implants according to our contemporary definition, it is in this area that polymethylmethacrylate as a biomaterial was born.

The material was formed into the desired shape either by thermoplastic means (injection moulding, press forming etc.) or in a "chemoplastic" way, i.e. curing a mixture of polymer and monomer in a mould at elevated temperatures. This is the way in which dentures are still fabricated.

The potentials of burrying the material in the human body had drawn the attention of investigators in these early years as well. Contzen et al. (1967) cites sources indicating that Clark and Wentsler had investigated the biocompatibility of polymethylmethacrylate in animal experiments in 1938 and found it suitable to be used for the repair of cranial defects. According to quotations of Kleinschmidt (1941) and Cabanela (1972) the first clinical application of the material in cranial defects was made by Zander in 1941. The fact that technology and medicine are particularly advanced in times of war, did not fail to apply to the development of biomaterials. The numerous casualities of World War II created a large demand for reconstructive and cosmetic surgery which is reflected by the many reports on correction and repair of facial injuries and deformities using acrylic resins in those years. (Wright 1944, Coffin, 1944, Marshal 1945, Murphey and Schlossberg 1945, Penhale 1945, Rivas and Izurceta 1945, Recalde 1944, Woolf and Walker 1945). In orthopaedic surgery the merits of "Plexiglass" or "Perspex" were explored, especially for treatment of coxarthropathy and in hip-arthroplasties (Scales and Herschell, 1945). In 1943 the Judet brothers started their experiments with hip endoprostheses, fabricated from plexiglass and they implanted the first prosthesis in 1946 (Judet and Judet, 1950). In 1940 and 1943 German and French patents were granted to Schnebel et al. for the use of tertiary amines as accelerators for the peroxide initiated polymerization of methylmethacrylate. The autopolymerizing cold-curing resins that could now be formulated, enhanced the possibilities in the already explored field and created new applications. At the beginning of the 1950's several dental restorative resins were available, which provided the dentist with an in situ curing material for the, at least initially, "invisible filling". Cranioplastic operations were simplified just like other reconstructive procedures because it was no longer necessary to prefabricate the inserts in gypsum moulds.

Another development resulting from the war was the discovery by Ridley (1951, 1952) that fragments of splintered airfighter canopies in the eyes of pilots were tolerated fairly well by the eye-tissues. Communicating this information to the manufacturers, Ridley learned that the canopies had been made of high purity polymethylmethacrylate. After this particular grade of material had been made available to the ophthalmologists, a succesful development of contact lenses and intra-ocular lenses could start.

The first large damp down on the enthousiasm around implant materials came in the 1950's when publications of the Oppenheimers (1948, 1955, 1958, 1960 and 1964) and Druckrey et al. (1954) mentioned tumor induction by polymers after implantation in animals. The interrup-

Table 1.1. Current clinical applications of acrylic resin implants.

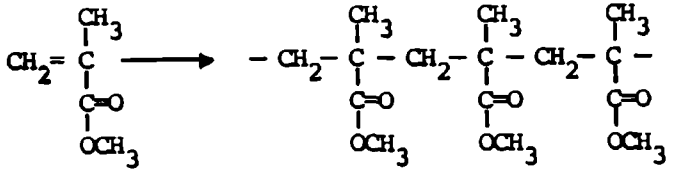
Skull	repair of cranial defects, correction of deformities	precured or in situ curing resins	Beumer et al. (1979) Cabanela et al. (1972) Al-Zain et al. (1973) Briggs (1973) Vaandrager et al. (1980,1981)
Ear,nose	external prostheses, correction of deformities	precured, plasticized precured resin	Chalian et al. (1971) Gonzalez Ulloa etal. (1964)
Eyes	repair or orbital fractures	self-curing resin or precured resin	Ballen (1964) Browning (1967) Frezotti et al. (1977)
	intra-ocular lenses	precured, high purity resin	Ridley (1970) Taylor et al. (1975)
Jaws	internal fixation of mandibular fractures, contour correction	self-curing resin	Pinkert (1975) Gasser (1970) Gonzalez Ulloa et al. (1964)
Teeth	tooth replica implants	various experimental resins	Hodosh et al. (1970,1972)
Thorax	correction of deformities	precured resin	Echapasse (1977)
Back	spinal fixation	in situ curing cement	Keggy et al. (1976)
Penis	penile inserts, testicular implants	precured resin, largely replaced by silicones	Loeffler et al. (1960, 1964)
Extremities	fixation of prosthetic joints, internal fixation of traumatic and pathological fractures	in situ curing cements	Charnley (1970) Harrington et al. (1976)

tion was of short duration however, as it appeared that possible carcinogenicity was related to physical aspects of the material like shape, dimensions, porosity, etc., rather than to the chemical composition of the materials. In addition, tumor formation could only be observed in certain animal species. Not a single case of malignant degeneration related to implants could be found in human beings.

The next and also last significant phase up to now in the development of biomedical acrylic resins arose in 1960, when Charnley (1960) revolutionized orthopedic surgery by introducing autopolymerizing resins as an anchoring medium for metallic hip endoprostheses. The term "bone-cement" was introduced and the following twenty years have been dedicated to refinements of implantation techniques, further assessment of biocompatibility, toxicological and allergenic aspects of polymethylmethacrylate and its components as well as to a gradual demarcation of the field of application. The development of other synthetic materials caused polymethylmethacrylate to be abandoned for certain applications in the past ten years, especially where the charateristic mechanical properties of the material (hardness, rigidity, low wear resistance, moderate strength, etc.) made it less appropriate for its purpose. However, in a broad area of dentistry and surgery acrylic resins maintain the position of established biomaterials. Table I summarizes, very incompletely , the main area in which acrylic resin implants are applied clinically today.

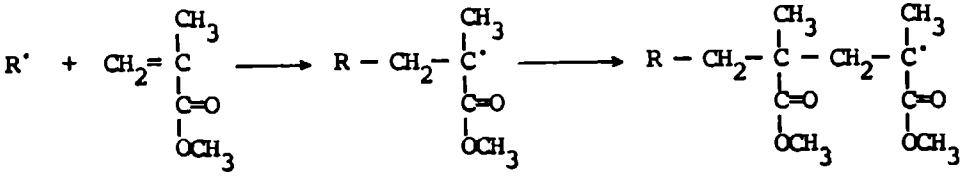
1.3. Chemistry of acrylic resins.

The polymerization of methylmethacrylate is a chemical reaction in which large numbers of the relatively small molecules are linked together into long chain-like molecules; monomer is converted to polymer:



methylmethacrylate polymethylmethacrylate

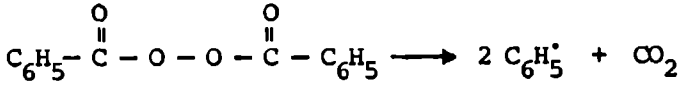
This is an organic reaction that takes place through intermediates which have an unpaired electron. Such intermediates are known as free radicals. When free radicals are generated in the presence of methylmethacrylate monomer, a radical adds to a double bond with regeneration of another radical:



free radical + monomer | initiated chain | growing chain

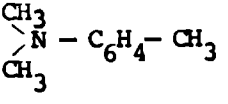
This regenerated radical is capable of adding to another monomer and so on, thus forming a growing chain. The propagation of chains continues until two growing chain radicals combine their unpaired electrons to one single bond and terminate each other.
Once initiated, the rate at which successive monomers are added to the chain radical, the polymerization rate, is very high. Up to thousands of monomer units can be linked together in a single polymer molecule in a few seconds.

The reaction commonly used to produce free radicals for the initiation of polymerization is the decomposition of dibenzoyl peroxide. When this compound is heated, is starts to decompose at about 60° C:



dibenzoylperoxide | phenyl radical

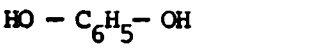
At room temperature, the decomposition of peroxides can be accomplished by a so called redox reaction with easily oxidizable compounds such as tertiary amines. In biomedical room temperature curing acrylic resins the commonly used accelerator is N, N, dimethyl-p-toluidine:



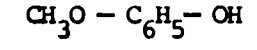
N,N,dimethyl-p-toluidine

The reaction with dibenzoyl-peroxide, delivering radicals for polymerization, is complex and also leads to the formation of such products as CO_2, secondary amines and amine oxides. Some of these by-products, especially the amine oxides, are coloured yellowish and this is the reason why room temperature cured resins are not so colourstable and transparant as heat-cured polymethylmethacrylate.

Besides the free radicals thus obtained, other, less controllable, sources such as light, radiation, oxygen and environmental heat can initiate the polymerization of methylmethacrylate. Thus, when the monomer is stored in pure form without any precautions, it has a very short shelf life and is often found to polymerize prematurely in its container. To prolong the shelf life of the monomer small quantities of a radical scavenger, the stabilizer, are added. Common stabilizers are hydroquinone or its monoethers:



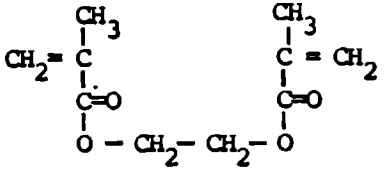
hydroquinone



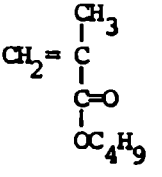
hydroquinone monomethylether

The stabilizing action of these compounds is based on the fact that they react faster with radicals than the monomer does, thereby being converted to quinone derivatives. When the monomer is cured, the first free radicals generated will be consumed by the stabilizer before the polymerization is initiated.

The properties of the cured resin can be modified to some extent by crosslinking the polymer chains. This can be accomplished by the addition of co-monomers having two double bonds. Such a co-monomer can be incorporated in two growing chains, which therefore become linked together chemically. When enough crosslinking monomer is added, the resulting polymer molecules form complex three dimensional networks of chains, rendering the polymer insoluble and improving some of its mechanical properties. The most commonly used crosslinking monomer is ethyleneglycol-dimethacrylate



ethyleneglycol dimethacrylate



butylmethacrylate

Other esters of methacrylic acid, especially ethyl- and butyl-methacrylate are sometimes added as co-monomers to improve working properties or to plasticize the polymer.

Most medical and dental acrylic resins are to be shaped and formed in situ or in moulds and are therefore available as a two component system: a powder which consists mainly of small polymethylmethacrylate spheres and beads and a liquid containing the monomer(s). For convenience of the user, the peroxide has been added to the powder component and in self-curing formulations the amine accelerator is

dissolved in the monomer. Prior to use, the powder and liquid are mixed in a ratio of approximately 2:1 w/w, and an easily mouldable dough is obtained, which cures in five to ten minutes if necessary, after heating in a gypsum mould.
For dental purposes, pigments and fillers can be added to the powder and surgical bone cements often contain some barium sulphate or zirconium oxide as radiopacifiers, because pure polymer is translucent for X-rays.

Table 1.2 gives the composition of a regular type of bone cement. Finally, it should be mentioned that the polymerization reaction is strongly exothermic. Consequently, after the polymerization has started, the released heat will cause the temperature of the curing dough to rise. The high temperature increases the polymerization rate, so that more heat is released per unit time and the temperature rises still further, etc. In this respect the term "cold-curing resin" is misleading, as the temperature centrally in larger masses of curing resin can easily reach values of 120° C. Advantage is taken of this process of autoacceleration in that it permits the polymerization to proceed to high degrees of conversion in relatively short time. In fact, the "snap-curing" behaviour of acrylic resins renders the material quite unique in comparison with other polymer systems. On the other hand, the temperature rise in room temperature initiated resins has disadvantageous consequences for certain applications in implant surgery, as will be discussed in section 4.1.1.

Table 1.2. Composition of mouldable room temperature curing[1] acrylic resin.

Powder	
polymethylmethacrylate[2] in spheres of 10 -150 µm	> 90%
dibenzoyl peroxide	2-3%
$BaSO_4$ or ZrO_2[3]	4-8%
Liquid	
methylmethacrylate monomer	85%
co-monomers (crosslinking agents; butyl methacrylate	10-15%
N, N, dimethyl-p-toluidine	2-3%
hydroquinone	50-100ppm

[1] heat-curing dental formulations are similar, apart from absence of toluidine accelerator
[2] sometimes co-polymer of methylmethacrylate and styrene or butylmethacrylate
[3] in dental formulations: fillers and pigments

1.4 Porous materials

During the past decade,there has been an increasing interest in porous implant materials. Growth of tissues into the pores of an implant has appeared to be possible if the diameter of the pores or the interconnection between pores in a sponge-like material is larger than a certain minimum. Although there is some controversion, this minimum most commonly is said to be about 100 µm for calcified tissues and about 10 µm for soft fibrous tissues (Klawitter e.a. 1972). Tissue ingrowth offers an attractive possibility of obtaining a mechanically firm connection between the implant and the tissues surrounding it. Especially in the case of implants in hard tissues, the fixation of the implants often causes problems, in particular when the implant has to bear mechanical loads. Apart from holding the implant in its place, the material-tissue interface has to transmit the stresses which arise when the implant construction is loaded and the stability of such an implant will thus largely depend on the mechanical stability of this interface. In this light,solid materials, with the exception of some glasses and ceramics, do not offer more than an intimate adaptation between material and tissue in the most ideal case. All efforts to obtain a durable adhesive (physico-chemical) bond between living hard tissues and a synthetic substrate have failed up to now. Fixation by screws or similar mechanical means concentrates the stresses on relatively small areas with the risk of bone resorption and loosening of the implant. It is increasingly understood that, given biocompatibility, a stable implant can only be obtained, if there is no mobility between implant and adjacent tissue and if there are no stress concentrations.

The problem of fixation is especially encountered in the area of replacement of diseased joints and teeth by artificial devices. A good example is provided by the replacement of hip joints. Although the first attempts to implant man-made devices in patients suffering from osteoarthritis of the hip were made as early as in the beginning of this century, the short and long-term results were rather poor, mainly because of the fixation problems mentioned above. The hip joint is a heavily loaded construction - forces of 3 to 4 times the body weight can be expected even during normal walking (Rydell 1966, Paul 1974) - and the available (metallic) materials which are strong enough to withstand resulting stresses of up to 100 N/mm^2 (Huiskes 1980) are about an order of magnitude stiffer than the bone to which the prosthesis has to be fixed. When the artificial femoral head is fixed directly to the residual femoral bone, which is mostly accomplished by an intramedullary stem, these conditions will easily give rise to stress concentrations at the interface between bone and implant. Due to this unnatural stress distribution the bone may resorb locally resulting in loosening and progressive instability of the implant. The failure rates of hip replacements dropped sharply after Charnley's introduction of acrylic bone cement (Charnley 1960). The material is used to form an intermediate layer between the prosthesis stem and the cortical bone; a large effective interfacial area between implant and bearing tissues is created by the cement

hardening in situ. From a mechanical point of view it, is expected and has been shown (Slooff 1970, 1971; Huiskes, 1980) that stress concentrations will be evened out by such a construction. Although the introduction of this cement created a number of new problems regarding the metal stem-cement interface and the mechanical behaviour of the cement itself, the total hip replacement changed from surgical experimentation to an operation routinely done at most larger hospitals.

Yet, the fixation of a hip prosthesis to the femoral bone by acrylic cement is an example of a situation in which only a very intimate adaptation of the material to the surrounding tissues is obtained and on the longer term loosening of the prosthesis is still a notorious complication (see e.g. Huiskes 1980 for an extensive review).

Also in prosthetic dentistry, the solution of the problem how to anchor abutments for crowns and bridges directly in or onto the jaw bone has not satisfactorily been solved up to now. Mechanical analysis (Tesk et al. 1973, Privitzer et al. 1975) has shown that the stresses induced in surrounding bone by the action of masticatory forces on metal endosseous implants can expected to be in the order of several MPa's. Large metal-to-bone contact areas by elaborate frames or fenestrated blades are used to distribute these stresses as much as possible.

Efforts to use an intermediate cement as in orthopaedic replacements have been made (Pugh 1976, Zarb 1972) but failed (Zarb 1979), probably also due to other reasons than mechanical overloading. In comparison with for instance hip joint replacements, dental implants are loaded to a comparable level of stresses but the total available area of contact between implant and bone is so much smaller, that similar misadaptations represent relatively much larger disturbances of the total available area and will thus result more readily in higher stress concentrations.

From a theoretical, mechanical point of view, a close adaptation of carefully matched materials could very well result in a stable implantation. However, bone itself is not a stable material. Due to the reactions of bone to the trauma of each operation, to the physical and chemical noxes of the implant materials and to the altered non-ideal stress distributions, the initial adaptation will become worse with time. When at least some remodelling of the surrounding tissues has to be expected after implantation of whatever kind of prosthesis and the initial contact between tissues and materials is very close, it should be envisaged that these tissues can only grow away from the impermeable surfaces of solid materials. Any tiny loosening leading to mobility, though small, between implant and bone will thus introduce new stress concentrations to which the bone may react with further remodelling and finally this process will result in loosening of the implant.

So, where remodelling of bone seems to be inevitable after implantation, it is a healthy concept to enable the tissues to remodel onto or into the implant. Here we have a very important, not yet fully explored, potential of biomaterials with a spongelike porosity: apart from the mechanical fixation as a direct result of the entanglement

of grown-in tissue and material, the multidirectional, three dimensional network of pores enables the ingrowth pattern to adapt itself to the stress situation or to remodel when conditions alter without loosening the obtained anchoring of the implant.

In other words, the fixation of hard tissues to a porous implant is, at least in theory, selfoptimizing and adaptable. In this light it is not surprising that a multitude of porous metals, ceramics, polymers and natural materials have been studied, developed and proposed as implant material during the past ten years.
Generally, the materials used already had a reputation as biomaterial - for instance because of biocompatibility - and the feature of porosity was added to accomplish better fixation possibilities.

In the literature,several methods have been mentioned by which the porosity was obtained. In the case of the high melting materials like metals and ceramics a porous structure is often obtained by sintering of powders. The physical shape and dimensions of the powder particles as well as the sintering conditions determine the geometry of the pores and their interconnections in a predictable and reproducible manner. Predictable pore geometry is also obtained when meshworks and fabrics of the material are compressed or laminated to the desired shapes like in some metals and polymers.

Less easy to predict is the process of foaming which is used to create porosity in certain ceramics and polymers. At the elevated processing temperature a gas develops, either by decomposition or evaporation of certain additives, leaving pores and bubbles on its way out of the material. In this case, the geometry of pores and their interconnections or even the presence of the latter depend on a larger number of variables and processing conditions, so that only an empirical relationship between conditions and structural parameters can be established.

A third principal method to obtain porosity consists of selective leaching out of a component which is present or has been added to the material. Porous ceramics ("Cerosium" Ross, 1970), polymers (Rijke 1977, de Wijn 1976, this work) and even metals (White 1975) have been developed in this way. Control of pore geometry is possible if the physical shape of the component to dissolve, the "pore-precursor", can be manipulated in a predictable manner,which most often is the case.

Finally, of course, there are materials in which porosity has been formed by non-human effort. The chorals of White et al. (1975) consisting predominantly of $CaCO_3$ and recently proposed wood implants (Bednar 1980) are, be it exotic, examples thereof.

Many of the materials mentioned may have reached in their development the stage of clinical, human,trial. Few, however, have gained general acceptance or are even commercially available for clinical applications. Perhaps the only example of an application in which the concept of porosity as a means to fixation is involved and which has become a familiar material in surgery, is polyester "velours"-fabric in vascular prostheses.
Other porous materials for implants in soft tissues that have or have

had some acceptance are Ivalon, a crosslinked polyvinylalcohol (Grindlay, 1951); Silicone sponges and "Proplast", a feltlike composite of polytetrafluoroethylene and Carbon (Homsy 1972, 1973). Porous materials for hard tissue implants or, rather, high stress situations have not reached the stage of commercial distribution, let alone clinical routine as yet. Several factors may cause this hesitation: the strength of porous materials is obviously lower than their solid pendants; fatigue strength might be inflicted as pores can act as ever so many stress concentrations; the long term behaviour of tissue that has grown into pores is still uncertain. Not in the last place, there is the fact that most of the proposed porous materials have to be formed and shaped prior to implantation. The initial fixation of the implant thus remains a problem akin to that encountered with solid implants. The advantage of fixation by bone ingrowth can only be enjoyed after a certain time and if a close initial contact between bone and implant has been accomplished. Especially in load-bearing implants initial stability of the implant tissue interface is thus again a necessity and may call for the same solutions as have been found in solid implantations.

An in situ forming material, a cement, with a porous structure would combine the benefits of initial stabilization and fixation by tissue ingrowth in the long run. Therefore, it might offer an attractive possibility, if the only cement that has been proved succesful in surgery, namely self curing acrylic cement,could be modified in such a way that it possesses a spongelike porosity after curing in situ. It has been the purpose of this work to realize and evaluate such a modification of self curing polymethylmethacrylate.

2.1. Review of principal synthetic methods

It has been briefly mentioned before, that the biocompatibility of polymethylmethacrylate has led to earlier and comtemporary efforts to synthesize the material in a porous form. In the following section the principal ways of synthesis and experimental results in biomedical applications will be reviewed and commented upon. Industrial methods and applications, if ever attempted, will be excluded from the discussion.

The first proposal to introduce porosity in biomedical polymethylmethacrylate came from Taylor and Smith (1972) who used the method of "sintering" of spherical particles. This process has in common with the familiar sintering of ceramics that,in compacting the powder,the particles are fused together only superficially and little material flow is involved. In this case, however, the fusion of the particles was not accomplished by high temperatures and pressures but by surface-softening the polymer particles with small amounts of monomer and compacting this mixture in a mould. Subsequent polymerization of the monomer at moderate temperature "solidifies" the obtained necklike connnections between the particles. A coherent material is the result.

Thanks to the fact that only little flow is involved in compacting the material, geometrical characteristics of the powder particles can be recognized in the microstructure. That also holds for the intersticial network of pores between the closely packed spherical particles. The latter fact means that the very important control of the pore geometry (pore size, interconnecting pore-size, and pore volume) can be achieved in a relatively simple way by the choice of particle size.

Klawitter et al. (1977) undertook an extensive exploration of the fabrication method and resulting materials. Depending on particle size and compaction pressure,materials with a wide range of pore sizes could be obtained. The range of pore volumes was restricted (22-32 volume percent) as this variable is obviously determined by the theoretical amount of free space between close-packed spheres (26-32% depending on packing lattice). As will be discussed in greater detail in a later section (3.2), it is remarkable that in spite of this small pore volume percentage,the pores are interconnected. A spongelike porosity is desirable because of the possibility of tissues growing in more than superficially, but from a mechanical point of view porosity will seriously inflict the strength of the material. The finding of a compromise between these two features will of course be facilitated when interconnection of the pores already occurs at low pore volumes.

The data of Taylor and Klawitter, however, show a dramatic decrease of strength values in these systems even in their relatively high density materials. Both compressive yield strength and ultimate tensile strength are reduced by 70-80% in the relevant range of porosity percentages as compared with the solid (biomedical) material. This will not leave very much room for optimizing purposes as the values of 20-30 MN/m^2 for compressive yield strength and about 10 MN/m^2 for ultimate tensile strength seem to represent the lower limit for practical purposes and can only tried to be increased. With reference to Park (1979), it is interesting to note that the relative strength values of these materials appear to coincide with the semi-empirical relation between strength and porosity volume which has been established for porous materials in general, regardless of the type. Also in correspondence with other reports is their finding that strength is rather independent of pore size.

In 1979 Peterson et al. reported about the biological evaluation of the material when used as a porous coating on the roots of dental implants in dogs. Their results can be divided into two catagories: success as to the biocompatibility of the material - which meant no rejection, no foreign body response, ingrowth of bone even in pores designed to be 50 µm on the average - and disappointment due to the mechanical weakness of the solid core material (also made of PMMA). Besides, the notorious problems at the permucosal passage,which render the results with dental implants so difficult to reproduce, also inflicted their success rates.

Nathanson et al. (1978) made similar observations on the biocompatibility of this type of material. This group reported even complete bony ingrowth into a material with an average pore size of 55- 79 µm,which is well below the critical limit of 100 µm for bone ingrowth as determined by Klawitter and Hulbert (1976).

A second principal route to obtain porous polymethylmethacrylate is the use of foaming agents. In the extensive work of Hodosh et al. (1965, 1969, 1970, 1972, 1974, 1976) on PMMA dental replica implants, two methods are followed to create porosity in the polymer with the purpose of obtaining mechanical retention after tissue ingrowth. The first method is the admixing of N, N'-dinitrosopentamethylenetetramine to a heat curing acrylic resin formulation, which is plasticized to some extent with n-tributyl phosphate. At the elevate curing temperature (220° C),the foaming agent decomposes, releasing nitrogen gas by which the polymer is foamed. Later on, Hodosh followed a method in which carbon and silica microballoons were supposed to "explode" by their expanding gaseous contents, thus creating pores in the resin. Although the Hodosh group claimed successful dental implants with these materials in animal and clinical applications, the method has found little or no response from other investigators. Apart from the largely unresolved problems which so readily cause the failure of clinical dental implants for reasons not specific for the material, the formulation chosen by Hodosh results in polymers without interconnections between the pores. For this reason tissue ingrowth can only take place at a very superficial level -

where pores occur at the surface - as was confirmed by Mathanson et al. (1978). After implantation of these materials in animal femoral cortex, thus excluding the reputed "dental" interferencing influences, the tissue response was found to be similar to the reactions on solid polymethylmethacrylate. Certainly the fact that materials with relatively low pore volumes had to be used (25% according to Gettleman et al. 1975) to preserve as much as possible of the mechanical strength of the polymer in these dental replica applications, will have contributed to poor interconnections between the pores. A random distribution of spheres (which gas bubbles in a polymer are) cannot be expected to show contiguity at a volume percentage of 25% (See also 3.2).

A third principal route to obtain porous acrylic polymers was presented simultaneously by Zaki and Kamel and by the author of this thesis in 1975 on the 7th Annual International Biomaterials Symposium held in Clemson. It concerns the leaching of water-soluble, solid or semisolid products out of the polymer in which they were dispersed prior to processing or curing of the material. The first two authors used NaCl particles and PMMA particles, the mixture of which was heat-compressed to solid shapes. Leaching out of the salt, as achieved by soaking the moulded samples in boiling water, resulted in a material with pores on the places were salt particles had been present. The strength of the obtained samples was claimed to be considerable (about 100 MN/m^2) at a porosity volume of 20%. In vivo test results were not given.

As stated earlier, however, a random distribution of particles at such low volume percentage cannot show frequent particle to particle contacts. This means that after leaching out of the salt, the residual pores will not be interconnected and the pores accessible for tissue ingrowth will only be found at the surface of the implants. An inherent disadvantage of the use of solid hard particles is that possible contact areas between the particles will be very small. These contact points will have to form the interconnections between the pores after the dissolution process. Although the pore size can be controlled easily by the choice of the particle size, the interconnecting pore size may very well prove to be, literally, a bottle-neck for tissue ingrowth.

The above mentioned synthetic methods essentially confine the clinical applications of the material to precured and preshaped implants. In this respect the possibilities of application should be sought in the same area where other porous materials that have to be prefabricated, like ceramics and metals, are attempted for implant purposes. Curiously, the described developments have exclusively taken place in the dental field and not in, for instance, orthopaedic or reconstructive surgery. Considering the biocompatibility of the materials, which is found to be good to excellent, and the ease of processing, the only rationale for the lack of interest from the surgical field can be the poor strength of the porous polymer. Of course, also, and maybe especially, dental implants ask for strong and rigid materials and objectively, one cannot think of one

reason why the choice should not fall on the available stronger materials in this field of application when the concept of "porous attachment" and the necessity of prefabrication are prerequisites.

The potential benefits of polymethylmethacrylate implants should rather be sought in the fact that this polymer can be formulated in the only in situ curing implant system that is known to be biocompatible: the cold curing or autopolymerizing acrylic resin as described in section 1.2.

The attempts to develop in situ curing porous acrylic resin have nevertheless been scarce. Apart from this work that was first presented in 1975 (de Wijn, 1976) the only other development that is known to the author, was published by Ryke et al. in 1977.

The latter group followed the method of adding solid, water extractable, particles of sucrose or tricalciumphosphate to a cold curing acrylic resin. They reported complete extractability of the filler when present in weight percentages larger than 30% (which would mean a volume percentage of about 15%!), a substantial decrease of the maximum curing temperature, decrease of monomer release during and after curing and, most remarkably, pore continuity after extraction in samples loaded with only some 15-20 volume percent particles. Unfortunately, the authors do not report actual pore volume measurements (e.g. microscopically) of the resulting material but give the various properties as a function of weight percent additives. The lower theoretical limit for interparticle contract, which is so important for this kind of systems will be shown to occur at higher volume ratios of particles (Section 3.2) and cannot be tested against the reported data. It is very likely that in these mechanically mixed cements the actual pore volumes are higher than can be calculated from the weight percentage data, because of air inclusion during the mixing process.

The interconnecting pore sizes in the cements, as measured by Hg-intrusion porosimetry, were smaller than the assumed critical limit for bone ingrowth (100 μm) up to high percentages of additives. As stated before this is the problem expected when hard solid particles are used.

The authors report tissue ingrowth after implantation of the cements in bone (femoral cortex of rabbits) but are not able to show that it concerns calcified tissue, which, because of the small interconnecting pore size, of course raises the suspicion that it was fibrous connective tissue.

Nevertheless, it shows that the concept of an acrylic cement with a porosity suitable for bond enhancement by tissue ingrowth is a workable one, despite of problems in proper dimensioning of the formulation.

2.2. PMMA-aqueous phase blends

The synthesis of in situ curing porous cement as described in this work follows the method of adding water extractable constituents. The difference with the other developments mentioned above consists of

using an aqueous phase, inmiscible with the uncured acrylic dough, that is dispersed through the polymer instead of using solid particles as an admixture.
The idea was born during an attempt to damp the notorious exothermic temperature peak of "cold-curing" acrylic resin by the addition of water, which should serve as a heat sink. It was noted that without the use of emulsifying agents, which was considered to be unacceptable for implant purposes, it was very difficult, if not impossible, to disperse the water through the dough with normal hand mixing techniques. Segregation of the viscous acrylic phase and the fluid water took place too rapidly. To overcome this problem, attempts were made to increase the viscosity of the aqueous phase by the addition of thickening agents or gelifying agents in the form of water soluble polymers. It was observed that if the viscosity of the aqueous phase was upgraded far enough in this way, the dispersion of the two phases in each other was achieved without any difficulty and, moreover, remained stable for periods surpassing the curing time of the acrylic phase.
The purpose of diminishing the temperature rise was effectively realised as will be shown in section 4.2 but it also appeared that if the volume percentage of added aqueous gel was high enough, the gel could be washed out of the cured cement leaving an interconnected network of pores. When these cements were implanted in the medullary cavity of rabbit femora, not only did the histological reactions of the bony tissues in contact with the cement compare favourably with the reactions to normal solid cement but tissue ingrowth had also taken place. After 5 to 6 weeks of implantation this tissue proved to be calcified (Feith, 1976). Apparently, the gel was biodegradable or at least extractable in vivo and could be replaced by living tissue.

2.2.1. Materials and methods in the synthesis of PMMA-aqueous phase cement.

Fig. 2.1. gives a schematic representation of the synthesis of this cement.

The acrylic resin used was a commercial acrylic bone cement (Sulfix-6, supplied by A.G. Sulzer, Winterthur, Switzerland) as is commonly used for the fixation of endosteal protheses in orthopedic surgery. It consists of a powder polymeric component and a liquid monomer and in so far does not differ principally from the traditional type of self curing resin. According to the manufacturers documentation, the powder component is a copolymer of methylmethacrylate and butylmethacrylate in the form of small spheric particles. Also the liquid monomer component consists of a mixture of 85% methylmethacrylate and 15% butylmethacrylate. The initiator system is the traditional dibenzoyl-peroxide/N,N, dimethyl-p-toluidine combination, added to powder and liquid respectively in concentrations of about 2%. The original clinical version of the material also contains 15% Zirconium oxyde, added to the powder component as a radiopacifier. As this compound appeared to disturb

an optimal functioning of the developed porous material, the manufacturer supplied us for experimental purposes with a sterile polymer powder without the radiopacifier.

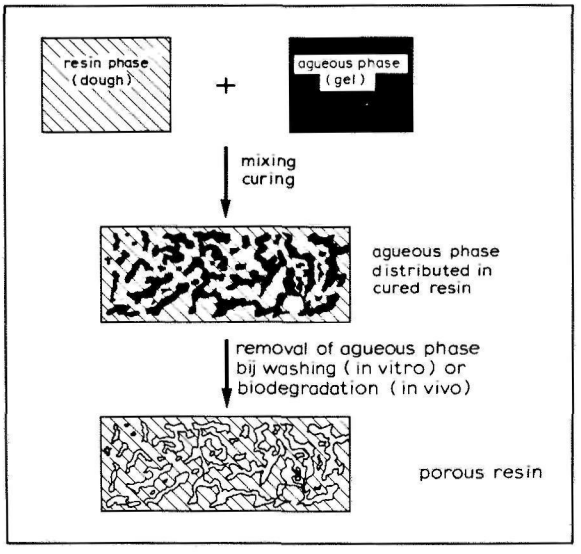
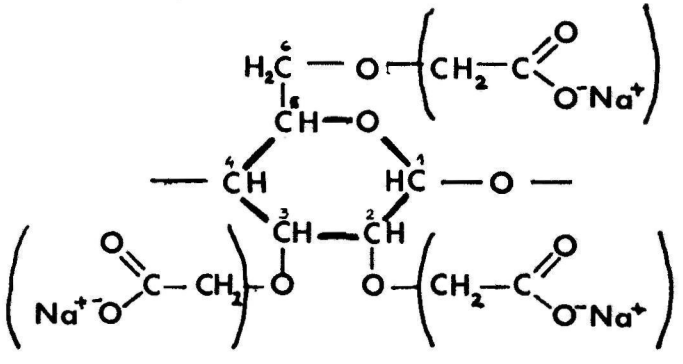


Fig. 2.1 Schematic representation of the creation of pores in acrylic cement.

For preparation of the aqueous gel, various types of water soluble polymers can be used principally, provided non toxicity and biocompatibility exist. One can think of polyvinylalcohol, which has had some reputation as an implant material, and of polyvinylpyrrolidone or Dextran-type polymers finding application in bloodplasma substitutes. In the experiments to be described, however, a carboxymethylcellulose derivative (CMC) was used. CMC is a well known commercial gelifying agent used extensively in industrial applications, food technology and pharmaceutical formulations. The basic structure of this polymer is:



The hydroxyl groups on C-atoms 2, 3 and 6 of the natural cellulose product are etherified with carboxymethylgroups (in parentheses). Although the degree of carboxymethyl subsitution can be controlled, complete substitution of all three hydroxy-groups cannot be accomplished. Therefore, CMC brands are available in various degrees of substitution. Together with the molecular weight of the polymer it determines the rheological properties of the prepared solutions and gels in a complicated way. A large advantage of modified cellulose polymers for our purpose is the high viscosity they cause at small concentrations in water as compared with other polymers mentioned before. A high viscosity of the aqueous phase in our cements is required to avoid gross segregation of the gel in the uncured dispersion,which would cause an irregular and uncontrollable pore size distribution in the cured cement. On the other hand, the gel, including the dissolved polymer is, expected to be removed by biodegradation under in vivo conditions from the pores. In that respect a low concentration of alien material is obviously desirable. Besides, high concentrations of solved particles which would be necessary in the case of the other polymers, or low molecular weight material, could lead to a high osmolality of the aqueous phase; this would not be in favour of biocompatibility.
The range of available watersoluble cellulosic polymers is tremendously large. It includes differently substituted polymers (methylcellulose and hydroxypropylcellulose for example) in various degrees of substitution, molecular weight, grain sizes, purities etc. Without having attempted to explore this area of materials exhaustively, the choice for application in our porous cements was made for a sodium-carboxymethylcellulose polymer known as Nymcell - ZHF 50 (N.V. Nyma, Nijmegen, the Netherlands). This particular brand has a (very high) degree of substitution of 1,18 and causes a viscosity of 390 cps when dissolved in water to a 1% solution. The gels used in our cements contained CMC in concentrations of 5-30% resulting in viscosities of many hundreds of thousands cps. Motivations for this specific choice were the fast solvatation of the powder particles by water, probably due to the high degree of (ionic) substitution, and the so-called "length" of the obtained gels.This latter property relates to the deformation of the gel that is possible before it breaks up in smaller fragments. Probably this low "gel-brittleness" is also due to the high ionic substitution of the polymer. In fact, the solutions of these cellulosic derivatives in water are highly colloidal in nature and the presence of many ionic groups along the polymer chains will enhance true solubility which will tend to diminish the mentioned gel brittleness. In the dispersions with acrylic resin this property turns out to result in more regular and smoother contours of the pores.
As received, the product is not suitable for implant applications; to this purpose it has to be purified and sterilized. Purification is necessary for removal of traces of metal salts and other low molecular weight substances. On laboratory scale this was accomplished by Soxhlett extraction with 96% ethylalcohol during 48 hrs. One way of sterilization of the product on a laboratory scale without

changing its properties too much (viscosity in solution) is by heating the powder in a dry environment of 120° C for at least 2 hrs but maximally 4 hrs.
A better method with regard to product properties is formaldehyde gas sterilization which is also used for sterilization of the polymer powder mixture in bone cements.

This method is a more elaborate one: especially the degassing of the powder at the low temperature required is a tedious procedure and more suitable for larger scale applications.

The modification of the traditional acrylic bone cement to a porous cement by aid of a gel involves the mixing of 4 components: the polymer powder, the monomer, CMC and water. In order to obtain a cement with optimum working qualities and mechanical properties, the sequence in which te components are mixed cannot be arbitrary. The following mixing schemes come into consideration:

1. Polymer powder and monomer are mixed; prefabricated gel is added and mixed into the dough.
2. Polymer and monomer are mixed; CMC powder is added and mixed into the dough and finally H_2O, which gels in contact with the CMC particles.

Both methods can be brought back to 3-component systems (two mixing steps):

1. polymer, monomer and gel
2. premixed powder of polymer and CMC, monomer and water

The only way to obtain a system involving a one step mixing procedure is to premix polymerpowder and gel to which the monomer has to be added when preparing the cement. Our experience is that method 2 gives the best handling characteristics and the most reproducible porosity patterns. Moreover this method appeared to give the best possibilities for sterilization procedures, prepacking considerations and probably, the best shelflife of the separate components.
In all the experiments that are described the polymer powder was premixed with the CMC powder in suitable proportions. This powder mixture can be stored in sterile conditions for prolonged time, provided exposure to light and oxygen is avoided as much as possible.
When preparing the cement the necessary amount of monomer is added to the powder and mixed by manual spatulating. When a homogeneous but still "sandy" mixture is obtained, the necessary amount of water is added and mixed through the acrylic mixture by, initially, careful spatulating. Spatulation is continued until the mixture is doughy, having a smooth appearance i.e.: until the two phases are no longer discernable by unaided visual examination. The whole mixing procedure can be accomplished in 2-3 minutes. After this, the dough can be handled in the same way as normal acrylic cement. Depending on environmental temperature, the cement will set in 8-10 minutes.

The manufacturer of Sulfix-6 bone cement prescribes a polymer-monomer ratio of 2,5 to 1 (by weight) for this cement. However, when the CMC powder is added to this mixture, the resulting dough becomes too dry. In order to assure a good moistening of the polymer component by the monomer in spite of the presence of CMC powder, we chose a polymer-monomer ratio of 2:1 by weight, i.e. relatively more

monomer than in the original cement. Apart from the polymer-monomer ratio,two other ratio's are of importance: the CMC-water ratio of the gel and the gel-acrylic ratio of the final mixture. So, the composition of a cement with 50% aqueous phase could be specified for example as: 50% by weight acrylic phase (consisting of 67% polymer and 33% monomer) + 50% by weight aqueous phase (consisting of 7% CMC and 93% water). For convenience,we will describe such a composition as "cement 50/7"; the first figure represents the aqueous phase content, the second figure gives the CMC content of the aqueous phase. It is not necessary to specify the acrylic phase composition because this has been 67% polymer and 33% monomer in all experimental formulations.
The examples in Table 2.1 give the compositions of 50/7 and 35/7 cement in weight units when prepared as a 3-component system.

Table 2.1 Composition of 50/7 and 35/7 cement

	50/7	35/7
Powder polymer	40 g	40 g
CMC	4,2	2,2
Liquid 1: monomer	20	20
Liquid 2: water	56,8	30

3.1. Introduction

In the previous chapter,attention has been paid to the methods in which pores can be created in solid materials,with some reference to the variables which influence geometrical characteristics of the pores,such as diameter and interconnectivity. Indeed, the accomplishment of the goals for which porous implant materials have been concipiated leans heavily on the control of these two structural parameters.
Together with the relative pore volume, the diameter of the pores, the presence or absence of interconnections between them and the diameter of the interconnections,the structure of the material is, according to the present knowledge,completely characterized for implant purposes. Other obvious characteristics of a pore structure as, for instance,shape factors and surface to volume ratio have not been recognized or explored as to their contribution to implant performance as yet.
In this chapter,the importance of the mentioned relevant structural parameters will be discussed in more depth,as well as the methods of characterization and their outcome for various formulations of the porous acrylic cement.

3.2 Pore-continuity

The rationale for the use of porous implant materials has been discussed in chapter 1 and can be summarized as:
- anchorage of the implant to the surrounding tissues by tissue ingrowth
- even distribution of stresses in the case of loaded implants by a large tissue-implant interface
- possibility of adaptation of the ingrowth pattern, and thus of the attachment, to the local stress situation.

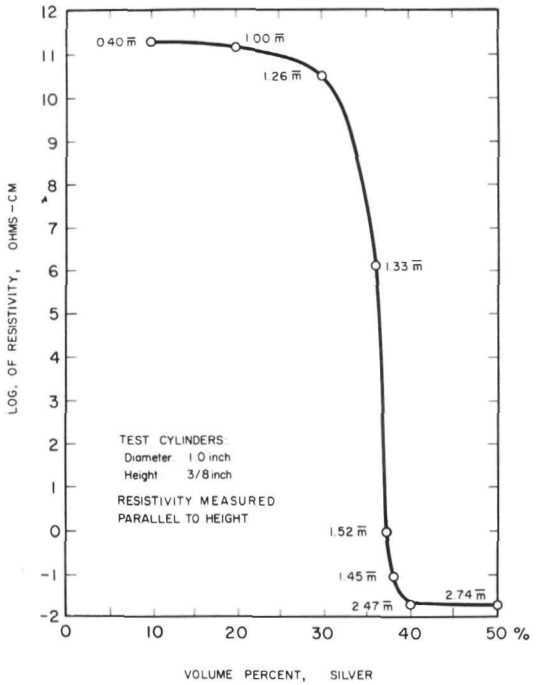
It is obvious that this integration of the implant in the biological environment would only be partially obtained when the porosity in the implant was of a closed type and tissue ingrowth could only take place in pores that are intersected by the implant surface. In fact, when superficial ingrowth would be considered to fulfill the needs satisfactorily,it would be wiser to design a solid implant with some kind of surface porosity.
When discussing the conditions for obtaining an open porosity in a material,two definitions have to be formulated. In the first place a "porous material" should be described as a material in which the probability to find a void has the same value in each finite volume element of (appropriate) relevant dimensions and which is equal to

the overall pore volume percentage, i.e. the total void volume is evenly distributed in the solid volume. Secondly, pore continuity should be regarded as the possibility to find infinite long paths of connected voids. If the porous material is regarded as a two phase mixture - a 'void-phase' dispersed in a solid phase - the theoretical treatment of the conditions for interconducting voids finds an interesting parallellism in the problem of obtaining electrical conductivity in composites of polymers and dispersed metal particles. Because of the promising industrial applications,this latter subject has received much attention by a multitude of investigators in the mid-century years.
For our purpose,we refer to the theoretical approach of Gurland (1962, 1966) and the more technical elaboration of Kusy and Turner (1971) and Scheer and Turner (1971).
Gurland (1962) studied the decrease in electrical resistivity of an insulating polymeric material by the inclusion of randomly distributed spherical particles of silver. At low volume percentages of silver,the resistivity of the composite was hardly affected but with metal loadings between 35-37 volume percent,the resistivity was observed to decrease sharply by several orders of magnitude. Microscopical examinations suggested the onset of infinetely long chains of connected particles at this percentage. In a theoretical treatment,Gurland (1966) reasoned, using the statistical theory of branching chains, that these indefinetely long chains would form abruptly when the average number of interparticle contacts exceeds the number of 2 per particle. In this statistical model, it is assumed that no more than one path exists between the two particles. In a physical mixture like the one under examination, however, there will be a substantial redundancy in interparticle pathways. This can be visualized by imagining a triangular cluster of three contacting particles in which each particle to particle "journey" can be made along two different paths. When this redundancy has to be taken into account,more complex statistical methods are required and were found by Gurland in percolation models. The outcome of this calculation predicted the necessity of only 1.3 -1.5 contacts per particle - depending on the particle lattice of the model - for the formation of infinite chains. Quantitative microscopical examination of the silver-polymer mixtures learned that this range corresponded very well with the measured values of interparticle contacts in the region where the drop of resistivity occurred.
Gurlands experimental results and examples of the microstructure of the mixtures are reproduced in Fig. 3.1 and 3.2. Returning on this point, to the problem of interconnecting pores,the importance of these results is obvious: When spherical voids occur at random in a material, interconnectivity cannot be expected at void volume fractions below 35-37%.
In the praxis of porous material synthesis,random void formation occurs in those cases where gas bubles or extractable, dispersed particles serve as pore precursors. For these systems it must be concluded that about 40 volume percent pores is a lower limit when

a perfusable open structure is desired because, physically, the voids must partly coalesce, rather than merely contact each other, to form interconnections of definite dimensions. Working on the electrical conducting polymer-metal composites, Kusy and Turner (1971) and Scheer and Turner (1971) indicated the possibility of obtaining non-zero conductivity at much lower metal loadings when the metal is not dispersed randomly through the polymer but in so-called segregated networks. When, for instance,the particles of an insulating powder are coated on their surfaces with a thin layer of metal, or preblended with metal powder of much lower particle size, and the polymer particles are subsequently compacted to a solid body, electrical conductivity is obtained already at a metal content of 6-8 volume percent. Statistical treatment of this case is not necessary; it is obvious that with ordered networks of metal an interconducting metal phase can be obtained, at least theoretically, at any low percentage in the mixture. Realization of such composites depends only on suitable techniques in which the ordered structure is maintained during the compacting procedure. Again, this metal polymer concept can be thought of to have a parallellism with the synthesis of porous materials. One of the synthetical routes described in section 2.1 is the superficial fusion of loose particles by heat and pressure or otherwise. In this sintering process the interstices are initially "ordered" around the particles and can be seen as a segregated network of voids which, depending on the subsequent compacting conditions, may or may not retain its interconductivity. The similarity should encompass also the possibility of obtaining an interconnective pore network at lower void volume than 35-37% as is the case in random pore distributions. In this light,the data of Klawitter et al. (1977),as reviewed in section 2.1,are of interest because their "sintered" polymethylmethacrylate spheres resulted in materials with open porosity at a void volume range of 22-32% thus supporting the validity of the above mentioned assumption.

The importance of low volume open porosity for implant materials can be found in the fact that pore volume and mechanical strength of the material correlate inversely. Although the possible extent of tissue-implant interaction is obviously smaller at lower pore volumes, the considerations given in this section must lead to the conclusions that synthetical processes involving the segregated void-network concept will offer the widest tange of possibilities to optimize material strength requirements and tissue-implant interaction.

Finally, it has to be remarked that the existence of lower volume limits for the formation of interconnecting pores does not mean that each system of pores exceeding these limits in volume is necessarily an open porosity. As the particulate voids have to coalesce to form interconnections,the condition is that the free energy of the matrix-pore (or pore precursor) interface is high enough to render such an event highly probable. Actually, many foams lend their insulating properties from the fact that, in spite of pore volumes up to 95%, the pores are separated from each other by a thin layer of matrix.



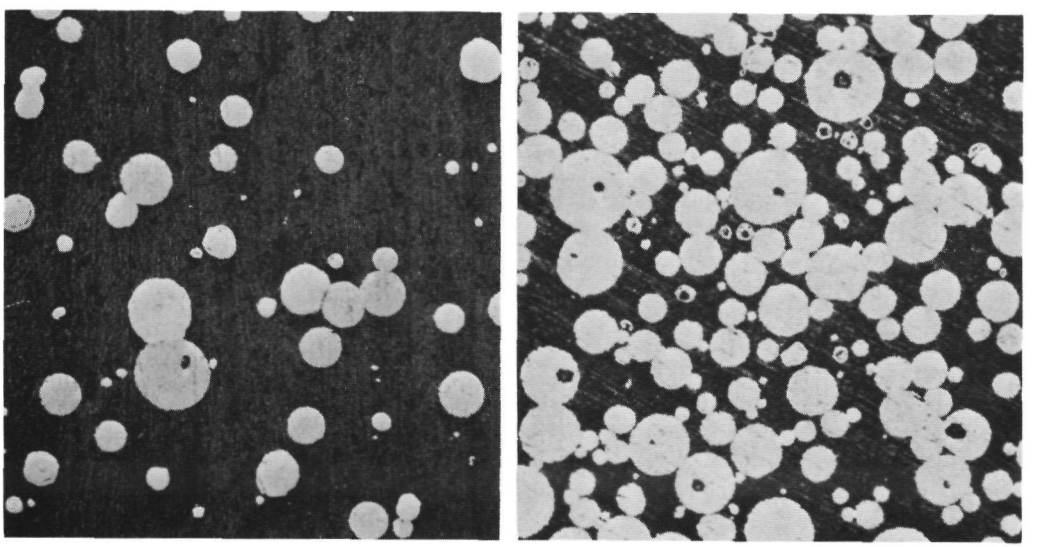


Fig. 3.1 (top): resistivity of bakelite-Ag composites as a function of composition and mean number of interparticle contacts ($\bar{m}$).
Fig. 3.2. (below): 10% and 40% Ag in bakelite (both figures from: Gurland, 1966. Courtesy, TMS-AIME).

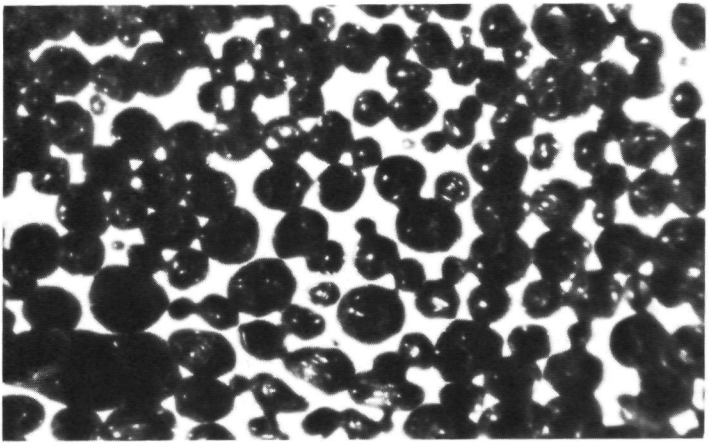


Fig. 3.3. Fotomicrograph of a section through polyurethane foam showing high pore volume (~ 75%) but isolated pores. The thin separating membranes were often destroyed by the polishing process.

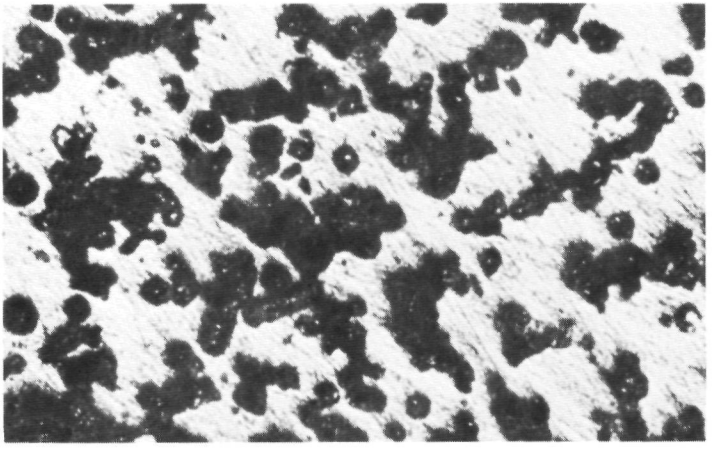


Fig. 3.4. Porous acrylic cement with a low pore volume (~ 40%) but interconnected porosity.

Fig. 3.3 and 3.4 show, for illustration, a polyurethane foam of high, closed porosity and an open porosity of much lower pore volume in polymethylmethacrylate respectively.
It follows, that some kind of test is needed to judge whether a system of pores is interconnected or not.

3.2.1. Measurement of pore continuity

Formally, when pores in a material are treated as a system of dispersed α-phase "particles" in a β-phase matrix, the methods of quantitative microscopy and stereology are applicable for the study of structural parameters as pore size and pore continuity. According to these theories (Underwood 1970), the degree of agglomeration between the dispersed particles can be expressed as the ratio between the surface of the α-phase particles that is shared with other particles ($S_{\alpha\alpha}$) and the total internal surface of the α- phase ($S_{\alpha\alpha} + S_{\alpha\beta}$):

$$C_\alpha = \frac{2\,S_{\alpha\alpha}}{2\,S_{\alpha\alpha} + S_{\alpha\beta}}$$

C_α is called the contiguity factor and ranges from 0 for completely dispersed to 1 for completely agglomerated α-phase.
This contiguity factor is measurable, and thus the degree of agglomeration can be expressed in a percentage, by quantitative microscopy. An array of test lines is superimposed on the pattern in a plane of section through the system and the number of intercepts per unit length of test line with interparticle ($N_{\alpha\alpha}$) and interphase ($N_{\alpha\beta}$) interfaces is counted. Then, it can be derived that

$$C_\alpha = \frac{2\,N_{\alpha\alpha}}{2\,N_{\alpha\alpha} + N_{\alpha\beta}}$$

Unfortunately, it is not possible to use this parameter for measuring the degree of interconnectivity of voids. When two voids contact, i.e. coalesce at least partially, the inter-"particle" interface is no longer discernable due to the very nature of a void.
For the same reason it is not possible in most cases to determine the average number of interparticle contacts as in the example of conducting composites given in the previous section. The conclusion must be that it is impossible to distinguish a closed porosity from an open porosity by simple areal quantitative microscopy unless the original shape of the single voids is retained and recognisable after partial coalescence. In cases of spheric gas bubles originated in viscous media or pores left after extraction of solid particles, this can be expected indeed.

Dealing with the problem of pore continuity, i.e. the probability of finding indefinite long paths of interconnected pores, reference can be made again to the statistical theory of branching chains. This theory does not only predict the average number of interparticle contacts necessary for the occurrence of infinite long particle

chains but also that it is highly improbable to find chains of moderate length; thus, a chain of particles or voids is very short or "infinitely" long. In the case of conductive composites, the validity of this hypothesis is supported by the sharp drop of resistivity at the critical metal volume percentage. Translated to the case of pores instead of particles in a matrix, this would mean that for all practical means, porosity in a material can be regarded as either open or closed. This also means that a test on interconnectivity may consist simply of some spreading phenomenon through the material, for instance the permeability for gases or liquids. If a fluid is observed to diffuse through a reasonable length of material, it is highly improbable that a more than negligible fraction of the pore volume is isolated.
The pressure which is necessary to force the fluid through the material is not relevant in this view, because this is determined by another parameter of the structure: the pore size, i.e. the dimension of the pore measured perpendicular to the direction of the passing fluid.

3.3. The pore size

The importance of the diameter of a pore in an implant material is that it determines the nature of the tissue which can grow into it. As the constituing elements of tissues (cells) have dimensions in the order of several microns, it is clear that the pores must provide sufficient room for their intrusion and development. For this reason ingrowth of the most primitive form of living tissue cannot be expected to take place at all in pores with minimum diameters lower than approximately 5-10 µm. For the development of more complicated types of tissue inward a substantial depth of the implant, the pores must not only provide room for cellular and extracellular constituents but also for small blood vessels which have to supply the essential ingredients for tissue formation and maintenance. So, because the different types of tissue vary in the complexity of their infrastructural organization, the pore size determines the kind of tissue which can form and exist in deeper parts of the implants and, within certain limits, the rate at which the tissue will grow into it.

Fundamental knowledge about the influence of the pore size on the kinetics of tissue ingrowth is still lacking. Neither has there been provided evidence to argue the experimental observations of Klawitter and Hulbert (1972) made 10 years ago indicating that no tissue grows in pores smaller than 5µ , fibrous tissues will grow in 5-15µ pores, osteoid tissue can occur in pores of 40-100 µ and mineralized bone needs pores larger than 100 µ. Although these data were collected from Ca-aluminate ceramic implants there is no reason to believe that biocompatible materials would influence the geometrical ingrowth conditions by their particular composition.

3.3.1. Determination of pore size

The direct microscopical determination of pore diameters in a system of multiply connected voids of complex shapes is complicated by the lack of a geometrical definition of the "diameter" relevant for tissue ingrowth and by the necessity of obtaining data of a three dimensional structure from a two dimensional plane of observation. In addition, not only the mean pore diameter of the system is of importance but also the distribution of diameters because every pore serves as a pore and, at the same time, as an interconnection between other pores. A pore that is large enough to allow tissue ingrowth may be excluded from the ingrowth pattern because it is connected to the rest of the system by pores that are too small for tissue ingrowth. Therefore, some parameter is necessary to predict the volume of pores that will accessible only via pores of a certain diameter.

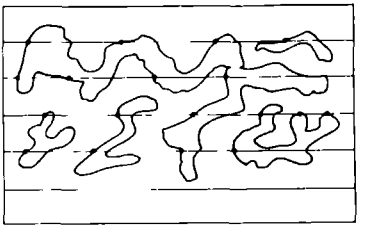


Fig. 3.5 Pores intersected by testlines.

Neither the mean pore size nor the distribution of pore sizes is directly obtainable from microscopical images of a plane intersecting a porous material. The methods of quantitative microscopy mostly consist of drawing a set of random rest lines through the plane of observation and counting intersections of these lines with phase boundaries. Fig. 3.5 gives a picture of some imaginary pores in a material matrix. The number of intersections in this example is 18.
As can be seen the testlines alternately intersect the pores and the matrix. It can be proven that the fraction of the total testline length (L_L) that intercepts the pores is equal to the volume fraction of the pores (V_V). A measure for the pore size is found in the mean length of the intercepts. If N_L is the number of intersections of testlines with pores per unit length of testline it can be easily seen that the mean intercept length, $\bar{L}$, is equal to $L_L/N_L = V_V/N_L$. The relationship between the mean intercept length and the actual size of the intercepted particles or pores depends strongly on shape factors. Table 3.1, compiled from data of Underwood (1970), gives values of the mean intercept length of sections through particles of various shapes.

Table 3.1. $\bar{L}$ for particles of various shapes

shape	actual dimensions	mean intercept length
sphere	diameter D	2/3 D
cube	edge b	2/3 b
cylinder	diam.D, heighth h	$Dh/\frac{1}{2}D+h$
spheroid (prolate)	axes b, 2b	1,46b
spheroid (oblate)	axes b, $\frac{1}{2}$b	1,28b
cylindrical rod	diam. D, length l, $l \gg D$	D
square rod	edge a, length l, $l \gg a$	a

Obviously, the mean intercept length as determined for pores is only a useful parameter when some reasonable assumption concerning the actual shape can be made. As interconnected pores have per definition one dimension - the "length" - which is large as compared with the "diameter" one can suppose some analogy with the rods from Table 3.1 and in that case the mean intercept length would be a good approximation of the pore size relevant for tissue ingrowth. Methods for the determination of the distribution of diameters from intercept data has only been worked out for very simple particle shapes as spheres. Obtaining a pore size variance from microscopical analysis should be regarded as useless because of the very simplified models that would have to be used for interpretation of the results. Microscopical characterization of a porous structure should therefore be confined to the determination of pore volume and mean pore size, the latter expressed as the mean intercept length.

A better method for determining pore size parameters that have predicting value for tissue ingrowth is mercury intrusion porosimetry. The method is based on the phenomenon that a certain minimum pressure is needed to force a non-wetting, liquid like mercury into a channel of capillary dimensions. The smaller the capillary the higher the pressure needed. The classical formula for capillary depression as cited by Ritter and Drake (1945) who developed the method, is

$$p.r = -2\ \sigma\cos\theta$$

in which p = pressure, r = radius of the capillary, σ the surface tension and θ the contact angle of the intruding liquid. For mercury σ = 0.48 N/m. The usual value for the contact angle is 140^{o}, although the wetted material will slightly influence this variable.
The quantitative relation between pressure and diameter of the pore then becomes:

$$D = \frac{1117.2}{P}$$

(D=diameter in microns and P=absolute pressure in cm.Hg)
A specimen of known bulk volume is placed in a picnometer with calibrated stem and evacuated in a vacuum chamber. The picnometer is filled with mercury after which the pressure in the chamber is increased gradually and the amount of mercury that intrudes into the specimen can be read from the picnometer stem. Thus, a graph of the pressure against intruded Hg-volume gives a cumulative curve, indicating which volume fraction of the pores is accessible at which pressure, i.e. through which interconnecting pore diameter.
The similarity between an intruding liquid and ingrowing tissue renders this technique particularly suitable for material characterization. If, for instance, bone is supposed to grow into the pores of an implant material, 100 µm is the minimum pore size required and Hg porosimetry can give the fraction of the pore volume that has an entrance larger than 100 µm thus being accessible for bone ingrowth. In this respect the often mentioned parameter "mean interconnecting diameter" is not so useful as it merely gives the pore diameter at which some 50% of the total pore volume is intrudable.

More senseful would be the determination of, for example, $v_{(100)}$, i.e. the volume fraction of pores intrudable by pores ≥ 100 µm.
A disadvantage of the traditional method is the limited range of pore sizes which can be measured. As the method was originally developed for other purposes, the upper range of commercial equipment is about 100-200 µm.

3.4. Control and characterization of porosity in acrylic cement.

As described in section 2.2.1 the pores in the developed gel-cements are predetermined by the dispersed aqueous phase. Therefore, the geometrical parameters of the eventual porous structure are largely determined by properties of this gel. Obviously, the total pore volume will be controlled by the fraction of aqueous phase in the starting mixture. The pore size will be determined by the dimensions of the dispersed gel micellae and dropletts which, in turn, will be related to rheological properties of the gel. A low gel viscosity, for instance, will enhance the coalescence of dispersed gel dropletts and this will leave larger pores in the material than in the case of a higher gel viscosity. Of course, the rate of segregation of the two phases is also influenced by the rheological and physical characteristics of the acrylic dough, the curing time and mixing technique. Actually, the geometrical structure of the porosity is determined by so many interrelating variables that this study will not deal with these matters on a more than phenomenological and qualitative level.

3.4.1. Pore volume and interconnectivity

The pore volume will depend on the volume of the gel which is added to the mixture. Fig.3.6 shows photomicrographs of samples prepared using increasing amounts of gel. Quantitative microscopical determination of the pore volume fraction - which is identical to the areal fraction in the plane of observation - learned that the measured values were systematically 8-10% higher than the weight percentage added gel. This can be explained by the specific weight of the acrylic dough which is approximately 10% higher (1,1) than the aqueous gel (1.0) and by the incorporation of air during mixing. Obviously, the enclosed air bubles will finally add up to the pores left by the dispersed gel after its removal.

To determine the minimum amount of gel that has to be added for interconnectivity to occur, the electrical conductivity of the cement mixtures was measured as a function of weight percent gel. In the mixture only the aqueous gel is conductive, so that any measurable conductivity of the gel can be caused only by interconnection of aqueous phase areas. Fig. 3.7 shows the cell and circuitry which was used for these measurements.
The results are shown in the graph of Fig. 3.8. Starting at about 24 wt.% added gel (32 vol.% porosity) the conductivity is seen to increase rapidly with concentration. Apparently, this is the lower

limit for interconnection of the dispersed gel phase; the correspondence of this value with the 35-37 vol. % critical limit as found by Gurland for conduction in silver-polymer composites (See Section 3.2) is remarkable but not unexpected when the structure of the gel dispersions is compared with these composites.

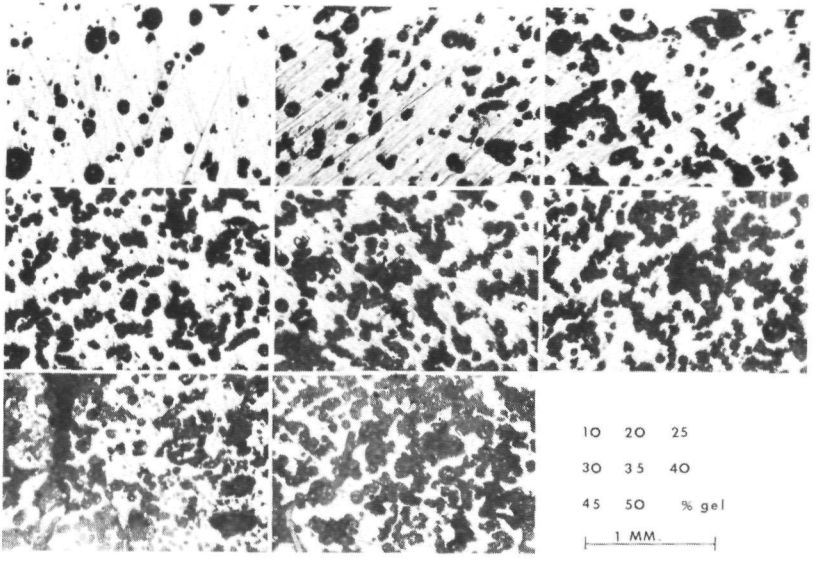


Fig. 3.6. Photomicrographs of samples prepared with various amounts of aqueous gel.

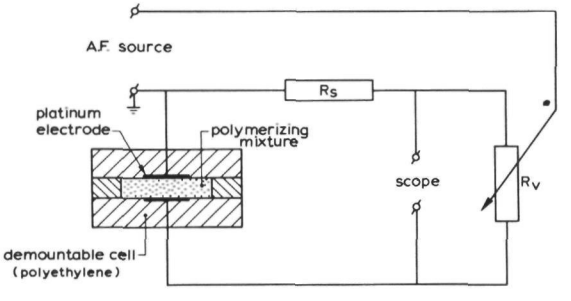


Fig. 3.7. Circuitry used for measuring the conductivity of the cement.

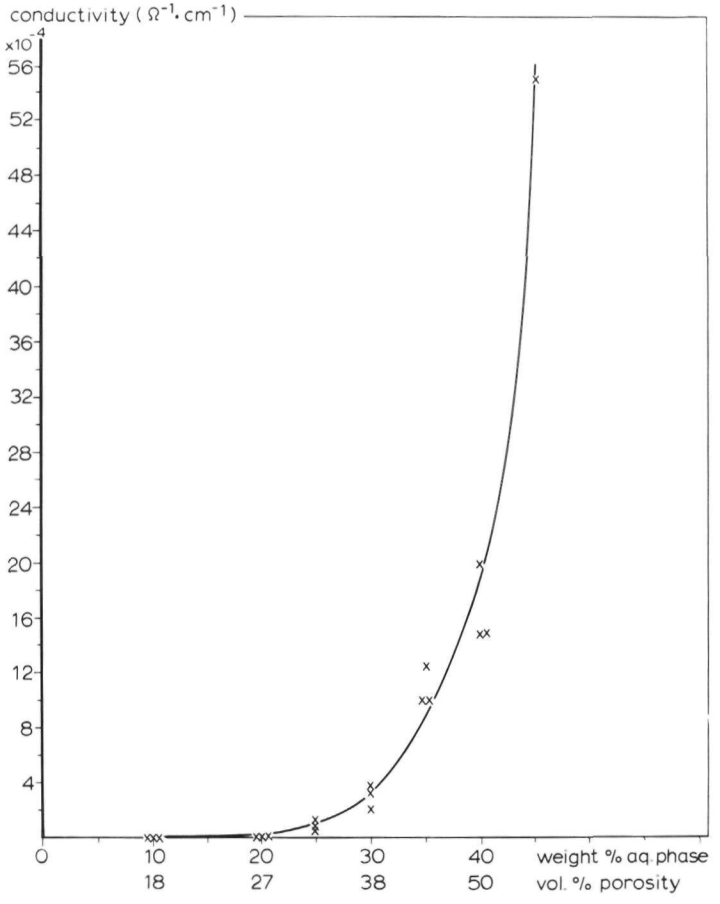


Fig. 3.8 Conductivity of the cement samples as a function of the gel volume

Fig. 3.9 Precipitated gel phase after dissolution of cement in acetone. From left to right: 20%, 35%, 40% and 50% aqueous gel had been incorporated in the cement.

Especially at low volume fractions the gel in Fig. 3.6 is seen to be dispersed as spheric "particles" not too different from the silver particles in the Gurland composites. At higher gel percentages, strings of contacting and partially coalesced spheres are observed. At still higher percentages increased coalescence contributes to a higher degree of interconnection and larger "pore" sizes. Very illustrating is a test in which cement formulations with varying gel percentages are dissolved in a solvent common for the resin and water but not for CMC (acetone, dioxane). Fig. 3.9 shows that at low gel percentages the precipitated CMC has the form of a loose powder but at percentages exceeding 35% by weight a coherent spongelike clot of precipitated CMC remains, proving the continuity of the gel phase in the original cement.

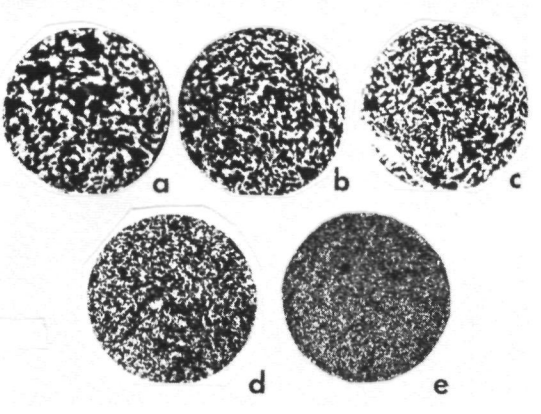
Interpretation of the data mentioned in this section leads to the conclusion that addition of 30 weight percent and higher aqueous gel to the cement mixture will result in dispersions with a continuous gel phase and thus, after removal of the gel, in a cement with an open interconnected porosity.

3.4.2. Pore size

The pore size in the gel cements can be influenced to some extent by the viscosity of the aqueous phase, which in turn is depending on the concentration of CMC. For illustration, Fig. 3.10 gives photomicrographs of specimens prepared with different concentrations of a specific CMC brand (Nyma, ZHF 50). Using quantitative microscopical methods, the mean intercept length $\bar{L}$ was determined of these specimens as a measure for pore size. Table 3.2 gives the obtained values.

Table 3.2 and Fig. 3.10
Pore size as influenced by CMC concentration

conc.CMC*(wt.%)	$\bar{L}_3$(μ)	in Fig.
5	600-800	a
7	500-525	b
10	425-450	c
15	350-400	d
25	< 200	e



*CMC: Nyma ZHF 50

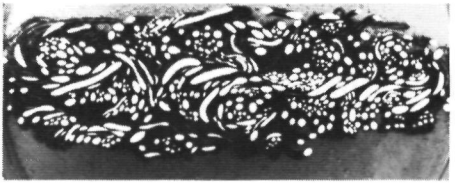
With reference to section 3.3.1, the interpretation of the mean intercept length depends on the shape of the dispersed "particles". To obtain some certainty about the meaning of the measured mean intercept lengths, the pores in the cements could be assumed to consist of a distribution of cylindrical capillaries. A model of such a system was prepared by embedding a mixture of copper wires of different diameters in cold curing polymethylmethacrylate resin.

The lengths and diameters of the used copper wires are summarized in Table 3.3. A photomicrograph of a section through this model is given in Fig. 3.11. The calculated mean wire diameter of this mixture is 400 µm (weighted by volume) and the mean intercept length, as determined by quantitative microscopy, appeared to be 404 µm. This result may be interpreted in terms of the mean intercept length being a reasonable good parameter to define a mean pore size in systems with capillary bone.

Table 3.3.
Length and diameter of Cu-wires which were embedded in pmma

Diam. (µm)	Length (cm)
200	196
300	154
400	100
500	54
600	22

Fig. 3.11
Specimen of Cu-wires embedded in pmma

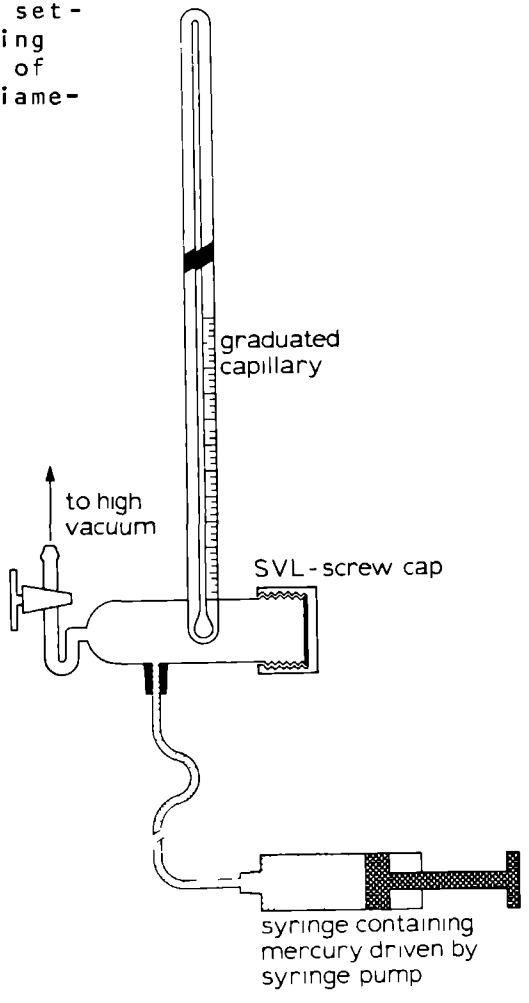


As mentioned before ,the mean pore size is not sufficient to characterize porous materials for implant purposes. The volume of pores that is accessible via pores having a minimum diameter of 100 µm should be determined by Hg-porosimetry. As commercial apparatuses are designed for measuring pores up to only 100-200 µm,which would probably be the lower limit of the range of interest in our materials, a special device was designed which should enable the determination of larger pore sizes.

The device as depicted in Fig. 3.12 consists simply of a glass container accessible by a SVL screw-cap and provided with a mercury inlet, an outlet to the vacuum pump and a measuring capillary. After evacuating the container and the capillary, mercury is introduced through a flexible catheter tube by a syringe pump operating at constant speed. The pump is placed some 75 cm lower than the measuring device, thus creating a mercury-lock to oppose the vacuum in the container. When a solid sample is placed in the porosimeter, the mercury rises in the capillary, after filling the container, at a constant rate. However, if pores are present in the sample the rate at a certain height of mercury, and thus at a certain pressure in the porosimeter chamber, will be lower than this "null-rate", because pores having a diameter corresponding with that pressure become "conducting" for mercury. The "null-rate" is resumed not until all the accessible pores are filled with mercury. If the time to fill the chamber with and without the sample of known volume is measured and the height of mercury in the capillary is recorded as a function of time, a diagram is obtained from which the pore volume fraction filled at a certain pressure and thus intruded through

certain pore diameters is easily calculated (Fig. 3.13 and 3.14).

Fig. 3.12 Apparatus and set-up for measuring distributions of larger pore diameters.



Factors limiting the measuring range of this device are: the dimensions of the sample itself,representing a certain height of mercury, the pressure needed to force mercury into the measuring capillary and non-zero vacuum conditions in the porosimeter. Calibrating the porosimeter with pieces of glass-capillaries learned that the designed apparatus measured pores smaller than 600 μm in reasonable correspondence with the relation given in section 3.3.1.
The porosimeter was used to determine interconnecting pore sizes in samples of the gel-cement prepared with 7, 10 and 15 wt.% CMC (ZHF 50) in the aqueous gel. The total pore volume was prepared to be 50%.

After hardening of the cement mixtures, the gel was removed by meticulously flushing with distilled water. The samples were wet grinded to dimensions of 25 x 10 x 7 mm and dried for 24 hrs. at 75° C. The porosimeter with the sample was evacuated up to residual pressures better than 100 µm Hg, prior to introducing the mercury.

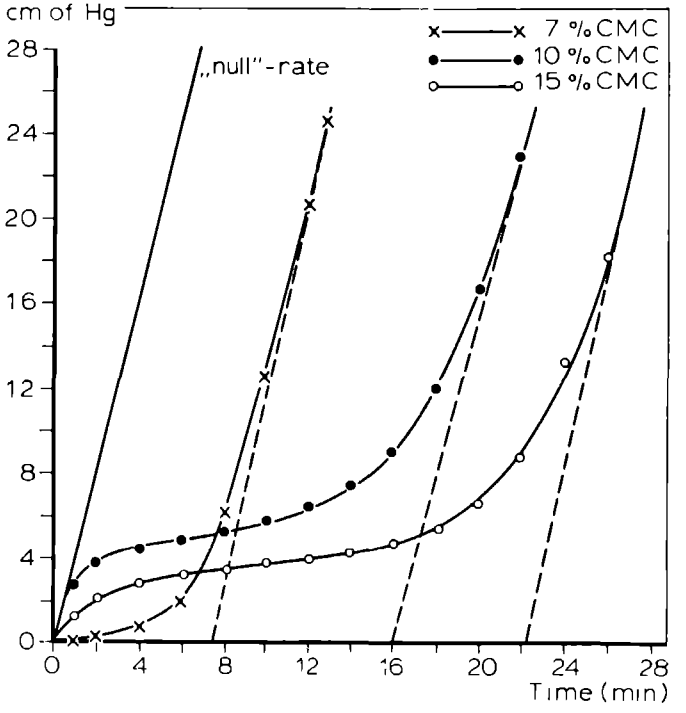


Fig. 3.13 Rise of mercury in the porosimeter capillary as a function of time for three cement samples with different pore sizes. The "null-rate" is the rate at which the capillary is filled in the absence of pores.

Fig. 3.13 shows the diagrams of curves obtained for three samples from which the cumulative curves of Fig. 3.14 were calculated. The curves clearly show the influence of gel viscosity of the intrudable porosity volume at different pore sizes. With 7% CMC-concentration, 90 volume percent of the obtained pore system is accessible through pores of 100-200 µm, the lower limit for bone ingrowth, compared with only 50-70% of the pore volume at the higher CMC-concentrations.

The importance of knowing interconnecting pore sizes instead of

overall mean pore sizes is also demonstrated. The cements prepared with 10 and 15% CMC concentration had a mean intercept length pore size of 350-450 μm (Table 3.2). However, only 20-30% of the pore volume would be intrudable at these pore sizes according to the results of Fig. 3.13.

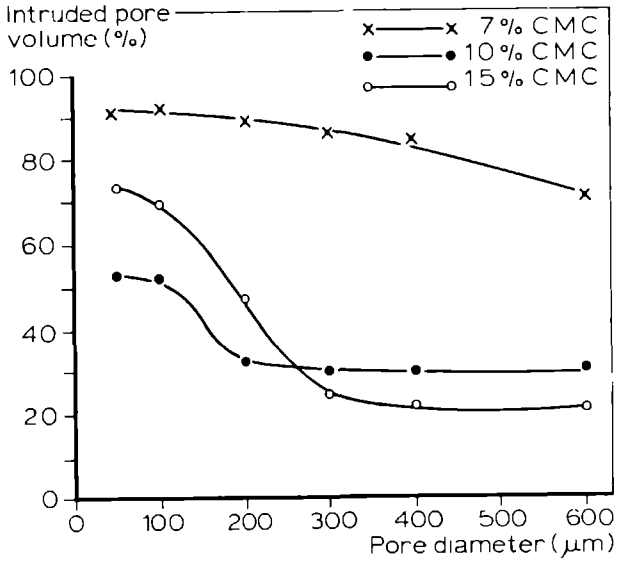


Fig. 3.14 Percentage of pore volume (vert. axis) that was intruded by Hg as a function of interconnecting pore diameter (hor. axis) for three different cement samples.

As will be discussed in chapter 5, cements prepared with 7% CMC in the gel appeared indeed to be invaded almost completely by bone when implanted in spongious bone of animal models. Cements with CMC-concentrations of 10% and more are never seen by us to contain bone tissue even after prolonged implantation times. Apart from the critical low interconnecting pore sizes in these implants, which might have prevented bone to grow in, the higher concentrations of alien material in the gel may of course have contributed to the observed lack of ingrown calcified tissue as well.

3.4.3. Other factors influencing pore geometry

The combination of these results and the biological response to be discussed later, has led to the selection of the 7% CMC-concentration,

- when it concerns the NYMA ZHF50 product - as the preferred composition of the gel. Unfortunately, we have no means at this moment to define the rheological properties of the used gels properly. In the first place the viscosities are so high and the solutions of CMC in water behave so non-Newtonian,that any determination of viscosity would be completely dependent on the measuring conditions and used apparatus. Secondly, in preparing the cements, the gel is formed during mixing of acrylic and aqueous components. As the dissolving process of this type of cellulosic materials is extended over a considerable period of time, there is no certainty about the stage of dissolution at the moment the pore size is determined,so that definition of viscosity values of a completely dissolved CMC-gel would be quite arbitrarily.

Reproducibility of the porosity pattern has appeared to be dependent on the ease and rate of dissolution of the CMC particles. The used ZHF50 brand has a high degree of substitution (1.2),which results in a large number of ionic groups along the cellulosic molecule chains. The occurrence of many ionic groups increases the rate of dissolution of the powdered material, which can easily be understood, but also diminishes the brittleness of the obtained gels. For the synthesis of the gel cement both aspects are of particular importance. The fast dissolution rate makes the gel viscosity less dependent on the mixing technique and low gel brittleness will enhance the coalescence of the dispersed gel regions,which will ensure the continuity of the aqueous phase and thus of the eventual pore system.
Indeed,experimentation with CMC brands of comparable viscosity but lower degrees of substitution resulted in cements with comparable mean pore sizes but poorer interconnectivity.
Also chemical breakdown of the highly substituted ZHF50, which occurs under influence of light and oxygen, leads to increased gel brittleness as indicated by the higher frequency of isolated pores in cements prepared using it. For illustration,Fig. 3.15 gives photomicrographs of cements obtained with CMC brands of higher and lower degrees of substitution as well as cement resulting from the use of deteriorated ZHF50.
Finally, some attempt has been made to influence the pore size in the cements by the particle size of the used CMC powder. The idea was to take advantage of the relatively low rate of dissolution of CMC particles as compared to the polymerization rate of the acrylic phase, so that the size of the CMC particles would still be recognizable in the hardened material. However, this method appeared to work only at high CMC concentrations in the aqueous phase and to result in a larger fraction of isolated pores due to poor coalescence of the partly swollen CMC particles. Therefore, this technique was abandoned.

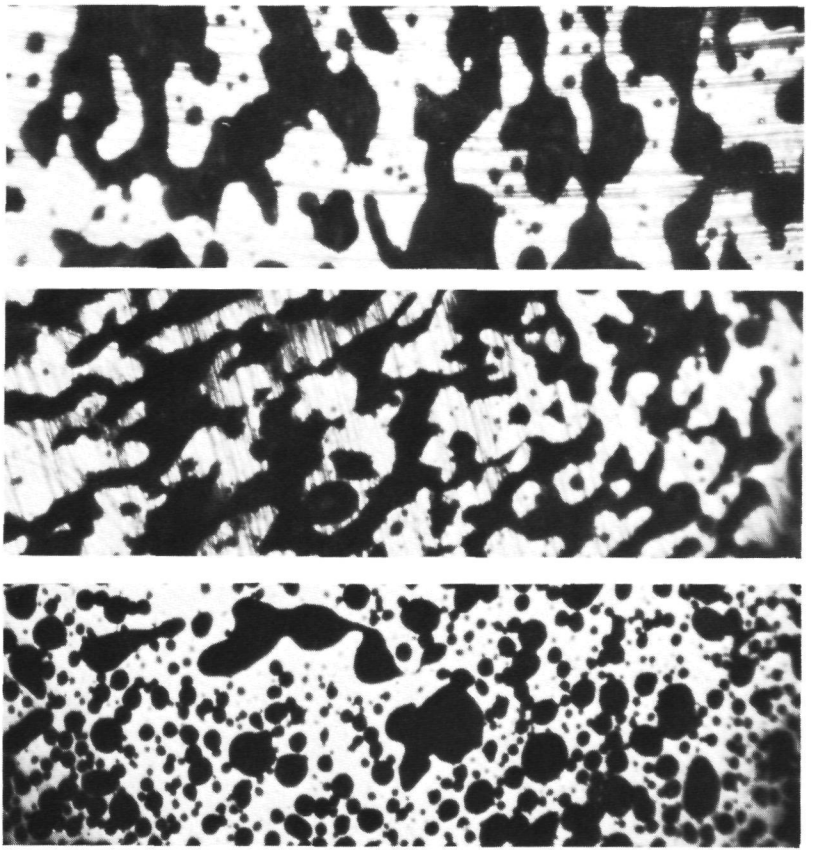


Fig. 3.15 Porosity resulting from the use of
A. CMC with a high degree of substitution (1.2; ZHF50)
B. CMC with a low degree of substitution (0.6; Courlose 1000)
C. Deteriorated CMC
(All samples same magnification)

CHAPTER 4. IN VITRO EVALUATION OF CHEMICAL AND PHYSICAL PROPERTIES

4.1. Introduction

The important properties of a potential implant material can be divided into two categories: properties relevant to the biocompatibility of the material and properties relevant to the proposed function of the implant to be fabricated. When dealing with in situ curing acrylic resin,there are two aspects falling in the first mentioned catagory being of special interest: the maximum temperature during polymerization of the material and the presence of low molecular weight constituents - especially residual monomer - in the cured material. As to the performance of acrylic cement implants,it is to be expected that particularly mechanical demands will be put on them,so that a good knowledge of the mechanical properties will be of considerable importance for the demarcation of possible applications.
In this chapter,laboratory experiments will be described characterizing porous acrylic cement respectively as to:
- maximum polymerization temperature and curing time
- residual monomer content
- rate of release of residual monomer
- mechanical properties

The discussion of these experiments in the following sections will be preceeded by a compendious review of the literature on temperature rise and possible thermal damage caused by in situ curing acrylic resins and on the toxicity of monomeric methylmethacrylate.

4.1.1. Maximum temperature in cold curing acrylic resin

As discussed in section 1.2, the exothermic nature of the polymerization reaction initiates a process of auto-acceleration in self-curing resins by which the temperature increases sharply. It will be clear that in situ curing of the resin may therefore result in thermal damage to surrounding tissues. The question is, to what extent damage will take place and whether it outweighs the advantages of the material as fixation medium or repair material. A satisfactory answer has not been given yet, apart perhaps from the fact that clinical application never has been upheld in spite of the widespread concern with the problem.

Uncountable are the reports dealing with measurements of the temperature peaks which occur in different areas of the curing resin mass. The possibly most quoted work is that of Ohnsorge et al., (1969A, 1969B, 1970) who performed measurements in laboratory set-ups and in cadaveric femora. The observed temperatures varied from 120° C in the centre of spheres to maximally 70° C at the interface between cement and (cadaveric) bone. In in vivo experiments,involving dogs and

patients, various authors found temperature peaks ranging from 45 to 70° C at the bone cement interface (Homsy et al., 1972, Meyer et al. 1973, Labitzke et al. 1974, Diehl et al. 1974).
The large scatter in the reported values is inherent to the subject in question; the temperature as a function of time and the eventual maximum temperature at a certain point, given a certain amount of released heat, depend on a multitude of parameters like geometry, coefficients of conduction, heat capacities, boundary conditions, etc., all of which may vary unpredictably from case to case and from individual to individual. The disagreement between investigators about the possible damage this temperature rise will cause in the surrounding living tissues is also very large. Histopathological investigations after clinical hip arthroplasty or animal experiments have been made extensively (Charnley 1970, Charvsky et al. 1973, Ohnsorge et al. 1970, Slooff 1971, Willert et al. 1972) but seldomly have given aequivocal answers to the question of thermal damage. Without an adequate experimental design it is not possible to distinguish between the histological reactions to the trauma of the operation, the cytotoxicity of the monomer and the tissue changes due to the high-curing temperatures of the resin. One of the few investigations in which an attempt has been made to discriminate between these possible adverse influences, was performed by Feith (1976). He operated rabbits by reaming the femoral medullary cavity and filling it with normal cement, a precured cement rod, non-curing cement dough, cement exhibiting low temperature peak due to heat-sinks etc. and concluded from his histological findings that the high polymerization temperature had to be regarded as a principal cause of histopathological reactions of the host tissues.
Yet, his findings cannot be generalized to every clinical application because of the specificity of conditions in the rabbit femur. Anyhow, the maximum temperature of the cement surface in vivo will be conclusive of any possible thermal tissue damage. In this respect great value is often attached to a critical limit of 56° C indicated by Lehnartz (1959) at which body protein is observed to coagulate or to a limit of 70-72° C at which Labitzke and Paulus (1974) found bone collagen to coagulate. These authors maintain that thermal necrosis need not to be feared as long as this limit is not surpassed. However, this seems to be somewhat oversimplified because not only the temperature but also the time during which a certain temperature value is maintained, should be considered to determine the probability of tissue damage. In a recent study on the subject, Huiskes (1978, 1980) reviewed investigations of Moritz (1947), Sevitt (1957) and Lundskog (1972) on thermal injury to various tissues in which temperature-time limits were determined for damage to epithelium, endothelium and the capillary system of the skin. On the basis of these and other data he constructed time-temperature limit curves for osteocyte necrosis and vascular damage in bone and designed a computer simulation experiment, using finite element analysis of a human total hip arthroplasty. The thermal parameters in the computer program were chosen in close agreement

with available experimental and theoretical data. Executing the program resulted in isotherms and time-temperature curves in the surrounding tissues following polymerization of the cement. By combining these data with the time-temperature limit curves,he was able to determine where tissue damage could be expected to occur. The prediction was that in certain areas of the acetabulum, provided a polyethylene cup is used, necrosis and vascular damage is likely to occur. In the femoral part no or only marginal thermal injury was predicted by this analysis. The results of this study and the poor reproducibility of clinical findings, may very well lead to the conclusion that regular polymethylmethacrylate bone cement is indeed only marginal as to its safety with respect to thermal damage.
Although it is possible to protect the bone against thermal damage by cooling it prior to applying the cement, the attempts to reduce the temperature peak should be considered of much importance. Generally speaking, this can be done in the following manners:
- reduction of the monomer-polymer ratio when preparing the dough;
- addition of inert compounds with high heat capacity (heat sinks);
- retardation of the polymerization rate.

The use of less monomer relative to polymer powder in preparing the resin would be a logical consequence of the fact that the amount of monomer determines the total amount of heat that will be released during polymerization. Huiskes (1980), using finite element analysis of implanted femoral prostheses, found a linear relationship between maximum cement temperature and total amount of released heat. Reduction of the latter (and thus of total amount of monomer) with 25% would result in a 15% lower maximum temperature.
Unfortunately, appreciable reduction of the monomer/polymer ratio in preparing the resin would seriously affect the working properties of the cement as the dough may become too thick and the curing rate may readily become too high for practical application.

The addition of substances with high specific heat is another sensible way to deal with the problem. Homsy (1971) claimed a substantial reduction of the peak temperature when titanium dioxide, stainless steal or carbon powder was mixed with bone cement. In his study,the result has been caused by two factors: increase of heat capacity of the resin and decrease of relative monomer content of the dough, both factors resulting from the addition of the heat sink. The most effective additive appeared to be titanium dioxide, a 15% addition resulting in a maximum temperature reduction of about 35% in a laboratory experiment.
However, also with this method the working consistency of the cement may be increased to an impracticle extent.
Another example of the heat-sink principle is the addition of a gel to the monomer/polymer mixture. Its effect will be discussed in section 4.2 when dealing with the properties of the porous cement.
The third approach is to decrease the rate of heat evolution by retardation of the polymerization reaction. Especially in the case of methylmethacrylate, the polymerization rate increases sharply as the viscosity of the system has surpassed a certain level. This phenomenon is known as the Trommsdorf effect or gel effect and

provides the cause for the auto-acceleration of the curing reaction. It is well known that the Trommsdorf effect can be reduced by the addition of other monomers and this is used in industrial large scale polymerizations in order to deal with the problem of overheating in the reactors. It has been shown by de Wijn (1974) that addition of certain co-monomers to the monomer of biomedical resins can considerably reduce the maximum curing temperature. However, in some cases lower degrees of polymerization were observed at the same time.

It should be borne in mind that the auto-acceleration of self-curing acrylic resins gives the materials their highly appreciated fast-curing character. Consequently, when trying to cope with the problem of temperature rise, the mentioned positive and negative aspects of the auto-acceleration can only be optimized.

4.1.2. Residual monomer

One of the draw-backs of biomedical acrylic resins when used as prosthetic or implant material is the possible contamination of the biological system with low molecular constituents, especially monomer, of the resin. The presence of monomeric residues in these resins is the result of the general phenomenon that when monomer is converted into polymer, the conversion will not be complete. The amount of unpolymerized material strongly depends on conditions during the polymerization such as temperature, dimensions of the polymerizing system, access of oxygen which acts as a polymerization inhibitor etc. In some applications of polymethylmethacrylate,monomer is formed by thermal decomposition of the polymer during high temperature processing of the material (hot pressing, injection moulding, for instance).

Monomeric methylmethacrylate has a solubility in water of 1.2-1.5% depending on temperature (Rauch et al. 1967) and when an acrylic appliance is placed in a moist environment such as a human body, this environment is contaminated with the monomer which will slowly be leached out of the polymer. Another, more severe, contamination is obviously encountered when in situ curing acrylic cement is implanted in the body and the system is temporarily exposed to the still uncured material.

The first reports dealing with the subject were from Deichman et al. in 1941 and Spealman et al. in 1945, who determined the lethal dose of monomeric methylmethacrylate when given intraperitoneally or subcutaneously to rats, guinea pigs and dogs. An LD_{50} of about 2 ml/kg intraperitoneally and 6 ml/kg subcutaneously was reported. These values appear to agree with more recent results of Homsy et al. (1969) - the lethal dose he reported for methylmethacrylate when given intravenously to dogs can be converted to 1.3 ml/kg - and of Lawrence et al. (1972) who found an LD_{50} of 0.9 to 1.3 g/kg when administered intravenously to mice. The cause of death in these experiments was ascribed to respiratory failure. This was confirmed by McLaughlin et al. (1973),who observed decreased pulmonary function (decrease of pO_2, increase of pCO_2 and decrease of blood pH) in dogs at a 75 mg/kg dose given intravenously. From this study it appeared that the lungs

functioned as the major clearing organ,which apparently caused it to be the first organ to fail.
Liver and kidneys were sometimes found not to be damaged to any extent by even excessive doses of methylmethacrylate (Wiltse et al. 1957), while others observed degenerative changes in the liver of animals that were exposed to vapors or large doses of the compound (Spealman et al., 1945, McLaughlin et al. 1973, Holland et al. 1973). Another problem is the possible influence of monomer on the cardiovascular system. After Charnley had introduced cold-curing resins as a fixation medium for total hip protheses in the early sixties, reports appeared in the literature describing moderate to severe, but transient, drop of blood pressure during the operation. This occurred immediately after insertion of the cement in the medullary canal of the femur. Even cardiac arrest on the operation table, causing death of the patient, was sometimes reported.

In his monograph on acrylic bone cement Charnley (1970) concluded from his own experiments and the already cited work of others that the often occurring fall of blood pressure (varying from none to 50 mm Hg) could not be related to the direct action of adsorbed monomer. He reasoned that the occurrence of the phenomenon was not reproducible, even not when one patient received two hip prostheses during the same operation. Moreover, it occurred preferentially after insertion of the cement in the femur, not after insertion in the acetabulum. Therefore, fat and air embolism.caused by forcing the cement into the medullary canal, should be responsible for the erratic occurrence of the complication. Indeed,emboli of fat, air and bone marrow were frequently found in the lungs, veins, arteries, kidneys and brains in cases where the patient died after the application of the cement (Kepes 1972, Herndon 1974). Prevention of embolism is a question of suitable technique and Charnley stated to have no worries about the intrinsic safety of methylmethacrylate in the blood stream.

Nevertheless, the monomer continued to be suspected as a toxic agent by surgeons, anaesthesiologists and investigators in pharmacological fields. This suspicion was undoubtedly based on the continuing stream of reports concerning cardiovascular and pulmonary complications that were associated with the use of bone cement during total hip replacements. It is impossible to cite only a reasonable part of the extensive literature that has been published on the subject during the past ten years.

However, the status quo is, in the opinion of the author, reflected by the work of the group of Lawrence and Autian (Lawrence, Mir 1973a, 1973b, 1974, Singh 1972) and of Petty (1977, 1978a, 1978b, 1978c) from which it becomes clear that esters of methacrylic acid are intrinsically toxic for various functions of the biological system. In high enough doses, these classes of chemical compounds exert not only an adverse influence on cardiac and respiratory functions but also on the immunological defence mechanism against bacterial attack and on the development of the fetus during pregnancy. The question is, whether the concentration of free monomer in the human body fluids can reach a level during and following clinical appli-

cations of the acrylic material, high enough to cause the mentioned effects to occur. Maximum monomer levels in the blood stream during routine total hip arthroplasty, which is undoubtedly the operation where the patient is exposed maximally, are reported to be in the order of 1 mg/100 ml. (Homsy et al. 1972, Pahuja et al. 1974, Modiq 1975). When this figure is converted to a human being weighing 70 kg and having a blood volume of 5000 ml it corresponds with a dose of about 0.7 mg/kg or 0.7×10^{-5} Mol/kg when injected intravenously. This is certainly well below the doses at which most of the significant effects were found in animal studies. At the moment, methylmethacrylate has been given the benefit of the doubt with regard to systemic effects in humans.

A special aspect of the biocompatibility of acrylic resins is formed by the fact that monomeric methylmethacrylate is capable of causing allergic reactions. The first reports identifying acrylic resin as a possible allergen appeared simulataneously with the introduction of the material in prosthetic dentistry. (Stevenson, 1941, Moody 1941, Goldman and Goldman 1944). Quite frequently, individuals who had received an acrylic denture, returned to their dentists with complaints of sore mouth, a burning sensation whether or not accompanied by objectively observable symptoms such as swollen oral mucosa, papules etc. This was diagnosed as allergic stomatitis in some cases. However, the observed symptoms were so confusing in appearance and clinical course that from the beginning hypersensitivity to the material was advocated and denied with equal zeal.

Very soon, it became clear that when the material was the cause of the symptoms, low molecular weight constituents of the resins and especially residual monomer had to be blamed for it and not the polymer.

One of the first systematic studies on the subject was that of Spealman et al. (1945) who observed a reaction in the form of mild erythema when the pure monomer was applied to the skin of human subjects. When the same subjects were tested again 7 to 10 days later by applying the monomer to another site of the skin, about 20% of them showed signs of erythema on the former testing site and apparently were sensitized by the monomer. These findings, combined with the observation that sore mouth problems were frequently met in patients who had received dentures made, rebased or repaired using cold-curing acrylic resin, sustained the idea of methylmethacrylate being an allergen. (Bradford, 1948, Vickers, 1949, Hollander 1951). When the dentures were removed or replaced by properly heat-cured dentures, the symptoms disappeared. This certainly is one of the essential characteristics of an allergic reaction: removal of the agent results in relief of the symptoms. However, so many other factors can be the cause of sore mouth problems. Mechanical irritation as well as physiological problems, for instance, can be alleviated by removing or remaking a denture. So, Nyquist (1952) was unable to find any allergic mechanisms underlaying the sore mouth problems of 248 patients.

Fisher (1956) indicated that monomeric methylmethacrylate is a sensitizing agent and could provoke an allergic contact-type eczematous reaction on the skin and oral mucosa. This was especially the

case in dentists and dental technicians who frequently have to manipulate acrylic materials. Here too, however, it was found that the incidence of allergy among denture wearers was very low. Turell (1966) concluded from his own work and that of others that methylmethacrylate is very seldomly the cause of allergic reactions. He ascribed the greater part of these reactions to cleansing agents, foods, drugs, etc., which are adsorbed by the denture base material in the course of time.

When acrylic resins became commonly used in orthopedic surgery, reports were made of surgeons experiencing pruritis and erythema of the finger skin after handling the cement during total hip replacemets (Peguin et al. 1971, Blair-Fries et al. 1975). Some complications in patients after hip replacements were associated with hyper sensitivity to the monomer (Kepes 1972), but Charnley (1970) doubted seriously whether obscure complications after using this material might be the result of some type of allergy.

Also in ophthalmology, where lenses and intra-ocular implants made of acrylic resins are used extensively, hypersensitivity to the material was not considered to be a major problem (Choyce 1964, Estevez et al. 1966). The discussion is still going on. In dentistry cases of "proven" allergic reactions to dentures continue to be reported. (McCabe et al. 1976, Giunta et al. 1976). In orthopedic surgery Monteny et al. (1978) concluded from studies on complement activity that methylmethacrylate could not be responsible when in cardiovascular complications an immunological process would be involved. In dermatology contact dermatitis due to esters of methacrylic acid is frequently reported (Malten et al. 1964, Sprechowitz 1971, Magnusson 1972, Emmett 1977, Marshall 1978, Hambly 1978, Marbach 1978, Rycroft 1977).

Overviewing the extensive literature on the subject, the question does not seem to be whether dermatitis types of reactions are provoked by direct action of methylmethacrylate or by the sensitization potential of the material. The problem is laying in the differential diagnosis to allergy in clinical cases. For this the following factors are responsible:

1. The inflammatory phenomena in the skin to be ascribed to an allergic reaction or to other reactions are quite similar. For example:
   a) the mechanical irritation of an ill fitting denture can lead to similar phenomena as an allergic reaction.
   b) the strong defatting action of the monomer enhances the possibilities of the skin or the mucosa to become bacterially infected.
2. The monomer content of acrylic appliances (seen as the true cause of possible allergic reactions) varies over a wide range from less than 0.5% in ophthalmological devices to several percents in cold-curing resin and depends, from case to case, strongly on the processing conditions, which mostly are unknown.
3. In the case of true allergy, its incidence almost certainly is very low and, consequently, very large groups of clinical cases have to be studied to obtain statistical significance.

Fortunately, the mentioned phenomena are not life threatening and therapy is relatively simple in most cases. Only a few reports have been made on serious consequences such as labour-disability of dental technicians (Fisher, 1956) or dangerous strokes of asthma (Stungis et al. 1969) following contamination by the monomer.

From the foregoing it will have become clear that it is of considerable importance to test the newly developed porous cement on its residual monomer content and on the rate at which it diffuses out of the material. The final decision concerning the clinical applicability of this porous cement strongly depends on the findings about these items in comparison with the values known for traditional solid bone cements.

4.2. Determination of the maximum temperature and curing time in the porous cement

From the discussion in the preceeding sections it becomes clear that there is no simple parameter which can be measured to predict the maximum temperature in clinical cases of implantation. Therefore, the porous cement and the solid cement have to be compared by a standardized test and the findings on the porous cement should be interpreted relative to the results obtained with the solid cement.

The experiments performed were very simple. The cements were cured in cells consisting of cavites measuring 15 mm in diameter and 15 mm depth made in polyurethane foam. In the center of the cavity a Fe-Const. thermocouple was fixed, which was connected by the usual circuitry to a recorder. The cells were placed in a water-bath thermostated at 37° C before and during curing. The time elapsing between the start of mixing the components and the moment the maximum temperature was attained, was taken as the curing time. In this way the maximum temperature and the curing time was measured for a series of cement formulations in which the volume fraction of aqueous gel ranged from 0 to 50 wt.%. Fig. 4.1.shows the values of the maximum temperature as a function of gel volume. The curing time increased slightly over the entire range: from 6 min. for a cement without added gel to 8 min. for a cement incorporating 50% gel. The effect of adding gel is clearly shown and not unexpected. Huiskes (1980), using finite element methods in thermal analysis, calculated the effect of adding gel on the maximum temperature rise in the cement and predicted values which are represented by the drawn line in Fig. 4.2. The measured values of Fig. 4.1 are adapted to this graph assuming qualitiy between volume percentage and weight percentage gel. The correspondence between predicted and measured values appears to be fairly good.

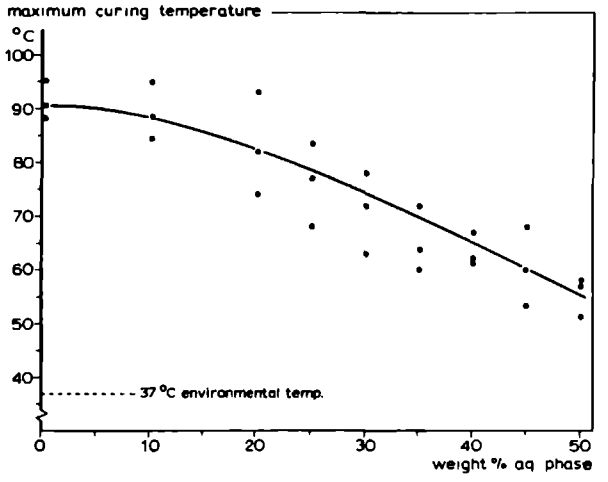


Fig. 4.1. Maximum temperatures during curing of the cements

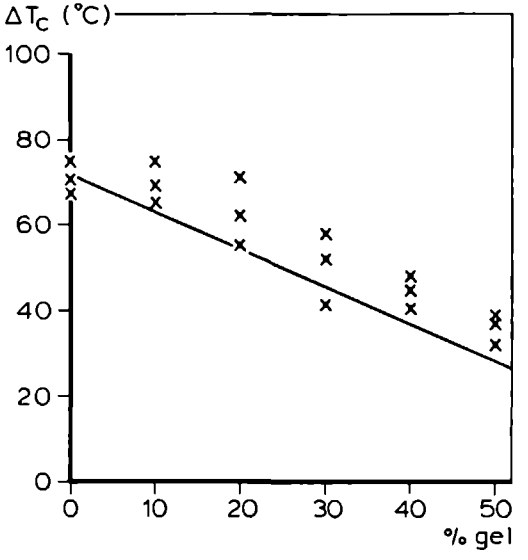


Fig. 4.2. Calculated (drawn line; from Huiskes 1980) and measured (xx values) of the maximum temperature rise in the cement mass as a function of % added gel.

4.3. Low molecular weight constituents of porous cement

4.3.1. Residual monomer in porous cement

As has already been mentioned, the fact that, after curing, biomedical acrylic polymers still contain a certain amount of residual monomer, is either due to incomplete polymerization of cold and heat curing resins or to thermal decomposition of the polymer during high temperature processing techniques. The latter phenomenon, which plays a role in the fabrication of ophthalmic lenses (Galin et al. 1977), is of no importance in the scope of the cementing materials described here.

The presence of residual monomer in polymers which have been polymerized in bulk, as is the case with biomedical in situ curing acrylic resins, can be explained by the fact that at higher conversion the viscosity of the system impedes progressively the diffusion of monomer to the growing chain ends. The overall rate of polymerization in radical initiated polymerization has been shown to be (see e.g. Bamford et al. 1958).

$$r = \frac{k_p}{\sqrt{k_t}} A\ [M]$$

(k_p is the rate constant of the propagation reaction, k_t the rate constant of the chain terminating reaction, A refers to the decomposition rate of the initiator and [M] is the monomer concentration). When the mobility of the molecules decreases progressively due to the increasing viscosity of the system, large deviations of the equation occur. The first effect is the already mentioned acceleration of the polymerization rate - the Trommsdorf effect - as the termination of the large chain radicals becomes diffusion controlled. In the following stage, at still higher viscosities, the propagation reaction is slowed down because of the decreasing diffusion rate of even the small monomer molecules. Finally, a situation is attained in which active radical chain ends occur together with unreacted monomer without the possibility of further reaction, however. The eventual quantity of the unreacted monomer will be determined by the temperature of the polymerizing system. Indeed, residual monomer contents in heat curing acrylic resins, as are used in the fabrication of dentures, have been proven to be significantly lower (<1% according to McCabe et al. 1976) than in cold curing resins such as bone cements (2-4%, Pinkert 1974, Brauer 1975).

In the light of the foregoing, the amount of residual monomer in our porous cement rises special concern because of two reasons: 1) the presence of the aqueous phase has been seen to reduce the exothermic peak temperature in the curing system; this can be expected to result in a lower degree of conversion as compared to the solid cement; 2) the solubility of monomeric methylmethacrylate in water is about 1.4% so that the aqueous phase in the porous cement can become saturated with monomer during the mixing of the components and during the time in which the cement is still uncured.
Thus, after curing, the cement as a whole contains residual monomer

in the polymer phase as well as in the aqueous phase and both percentages may end up in a higher level than is found in solid cements.

The analysis of the monomer content of the porous cement is complicated by the heterogeneity of the system. Although it is possible to dissolve a freshly cured sample of the cement in a solvent common to the polymer and the aqueous phase - e.g. acetone or dioxane - analysis of the solution by gaschromatographical methods should be regarded as unreliable. The polymer component should be expected to decompose in monomeric fragments at the high column temperatures that are necessary, thus leading to erroneous results. Infrared analysis of the monomer in such a solution is hampered by the presence of water, which interferes at the 1645 cm^{-1} absorption maximum of the double bond.

It was decided to analyse the phases separately. After washing out with water, the aqueous phase was analyzed by a titrimetric method with Pyridine Sulphate Dibromide and Mercuric Acetate catalyst as described by Vogel (1958).
After washing and drying, the polymer phase was dissolved in chloroform to make a 10% by weight solution. Hereafter, this solution was analyzed on a Perkin Elmer 457 Infrared spectrofotometre , using a demountable cell with AgCl windows and a path length of 1 mm. The peak height in transmittance units of the maximum at 1645 cm^{-1} (C=C stretching vibration) was calibrated using the left, short wave, shoulder as a fixed baseline (80% Transmittance) reference (Fig. 4.3). 12 samples of freshly cured 50% porous cement were analyzed in the manner described. It appeared, however, that only the aqueous phase analysis could be performed satisfactorily. The mean content of this phase was found to be 1.7% by weight with a standard deviation of 0.6%. This result can be interpreted in terms of saturation of the aqueous phase with monomer (1.4% by weight as determined for the Sulfix monomer mixture in water of 22° C). The experimental error and variance is largely due to uncertainty about the exact amount of aqueous phase in the sample which was assumed to have the theoretical value of half the sample weight.

Drying of the polymer phase after removal of the aqueous phase, to prevent remnant water to disturb IR-analysis, appeared to ask for vigorous drying conditions, which was feared to inflict the residual monomer content as well. Therefore, it was chosen to dissolve whole samples immediately in chloroform and to dry the obtained solution, containing a few dispersed dropplets of gel, using corned $CaCl_2$ as an exsiccant. This proved to be an effective way to get rid of remaining water. Six samples of 50/7 cement thus analyzed, showed a mean residual monomer content of 1.9% by weight (standard deviation 0.2%).
Determination of the residual monomer in solid Sulfix specimens, prepared by mixing polymer and monomer in a 2:1 weight ratio, by the same IR technique resulted in values of 2.8 to 3.0% by weight, shortly after curing.
At this point we have no explanation for the fact that the polymer

phase of the porous cement appears to be lower in residual monomer content than solid Sulfix cement. Also, when the content of the aqueous phase (1.4%) and the content of the polymer phase (1.9%) are averaged to obtain a value of 1.7% for a cement with 50% gel, the porous cement appears to compare favourably with the solid cement.

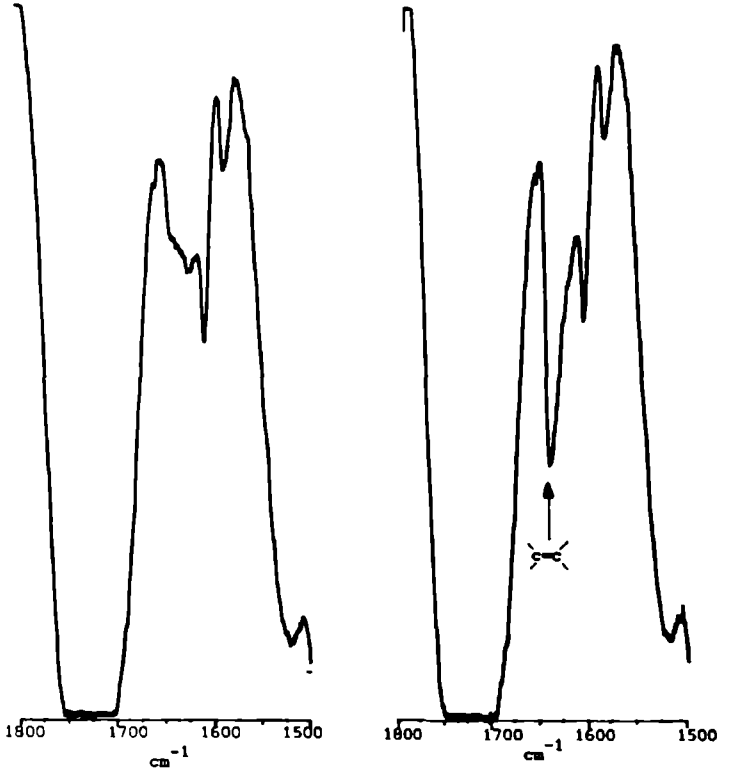


Fig. 4.3. IR spectrum of PMMA solutions in chloroform without (A) and with (B) residual monomer.

4.3.2. In vitro determination of monomer release from the cements

The presence of residual monomer in acrylic resin is only of concern because of its release from the resin into the biological environment. In this respect,the exact value of the monomer content is of less importance than the rate at which it leaches out. There are two reasons to expect that freshly cured porous resin will

release monomer at a higher rate than solid resin:
- the large increase of specific surface created by the pores will facilitate monomer diffusion
- the initially present gel will contain about 1.4% monomer (section 4.3) and this aqueous phase is supposed to diffuse out of the pore system at relatively high rates.

Again, the cements can only be compared with each other in this respect by submitting them to a standardized in vitro test. This test was found in curing a constant amount of cement (1.5 g) in the form of a flat disk measuring 25 mm in diameter and 2.5 mm thick in 50 ml of water at 37° C.
The water was discanted and renewed at time intervals ranging from 0.5 hr. to 10 days. The monomer content in the supernatant water was determined by extraction with n-hexane and subsequent gaschromatographical analysis. An Packard Becker 419 instrument was used, fitted with a 3m x 1/8'' stainless steel column containing Chromosorb WAW/DMCS, 80-100 mesh, coated with 25% Emulphor 870. The column temperature was 140° C and N_2 was used as a carrier gas at a flow of 7 ml/min. Ethylmethacrylate was used as an internal standard.
The graph of Fig. 4.4. shows the cumulative results for a 50/7 porous resin and two commercial solid resins (Sulfix 6, Sulzer Bro's, and Palakos, Kulzer).

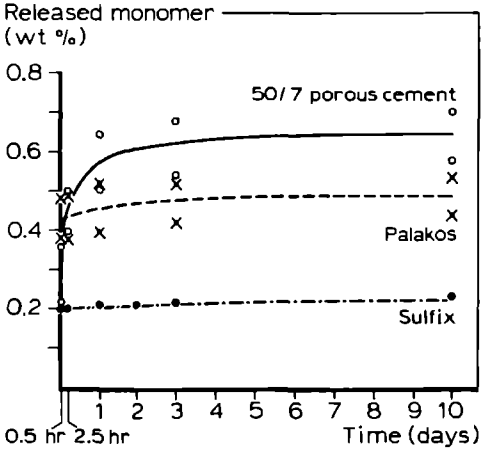


Fig. 4.4. Amount of monomer (% of sample weight) which has leached out of porous and solid resins into the aqueous environment.

At the first sampling moment, 0.5 hr after the still uncured cement was brought into contact with the water, no significance can be assigned to differences between the various cements. The results here depend largely on the condition of the dough at the moment of immersion.

However, the expected higher rate of release from the porous resin is confirmed by the values found at periods up to three days after curing. At the longer term, there seems to be no appreciable difference in release rate between the solid and the porous cement. The eventual amount of monomer released by the porous resin (0.6-0.7%) can be completely explained by the expected content of the aqueous phase as these samples consisted for 50% of a gel containing 1.4% of monomer. Apparently, the higher monomer release rate in the first days as compared to a solid resin is predominantly caused by the saturated aqueous phase leaking out of the resin, the larger surface of the resin itself being of undetectable influence on the longer term release of residual monomer. Measurements over still longer periods were seriously hampered by the instability of aqueous monomer solutions. Due to evaporation, hydrolysis and/or polymerization the monomer content of control solutions appeared to decrease by more than 50% when stored at 37° C for 3 weeks. Therefore, and because of the very low release rates of all the tested cements, such longer term measurements were considered to be of no value.

4.3.3. In vitro determination of CMC release from porous cement.

To gain insight in the rate at which the gel will disappear from the pores of the cement, thus making place for tissue to grow in, cements with various gel formulations were submersed in water at 37° C. Samples of the supernatant were evaporated to dryness and the residue, consisting predominantly of CMC, weighed. The cement specimens were cylindrical, 26 mm in diameter and grinded to a thickness of 5 and 10 mm. From the liquid sample volume and the residue weight the total amount of released CMC could be calculated. The results, measured over a period of 6 days, are given in Fig. 4.5. The graphs show that in all cases the CMC release rate has dropped to very low values after 3 days. In that period the released CMC also approaches the theoretical maximum indicating completeness of the diffusion process. Actually, this theoretical maximum is exceeded slightly in most cases, which is due to debris remaining in the pores after grinding the specimens. This debris will have contaminated the first residue, rendering it too high.
However, the absolute values are of less importance than the release rates and apparently the diffusion rate is so fast that the expected differences between specimens of various thickness and gel concentration and thus various pore sizes are only observed in the first 2 days.
The results sustain the observations made with the monomer release in the previous section. Those rates also indicated that the aqueous gel diffused out of the pores in approximately 3 days.

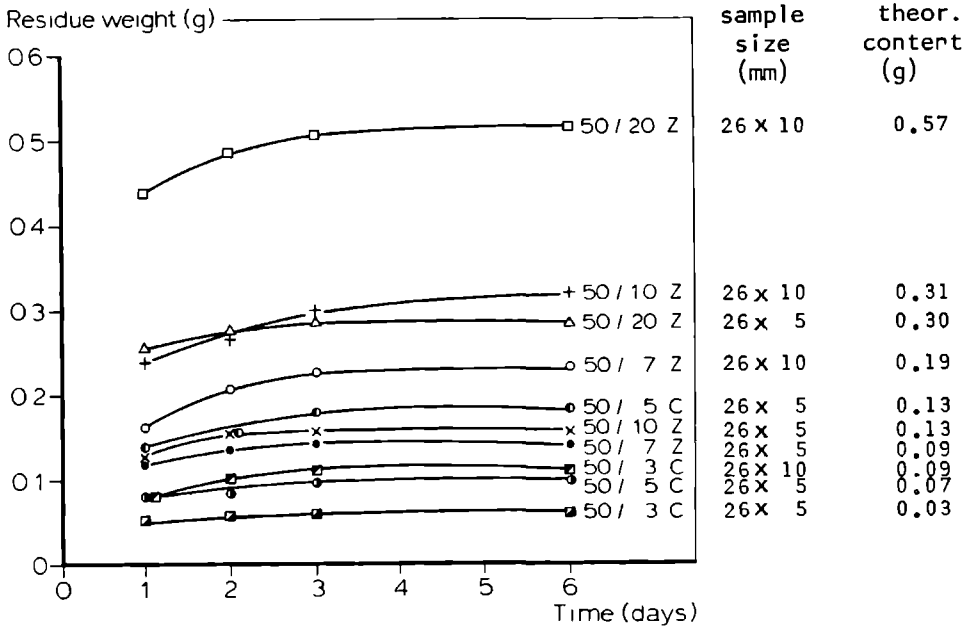


Fig. 4.5. Weight of CMC that has leached out of porous resins of various compositions and various sample sizes.

4.4. Mechanical properties

4.4.1. Introduction

The mechanical properties of porous materials are obviously compromised with respect to their solid analogues. There are two ways in which pores in a material can inflict the mechanical properties:
1) by diminishing the material volume in which energy can be dissipated or the area over which forces can be distributed and
2) by causing stress-concentrations
With respect to the correlation between e.g. strength (S) and pore volume (v) the first mentioned trivial effect can be expressed mathematically as:

$$S = S_o(1-v^{2/3})$$

However, usually a faster decrease of strength with increase of pore volume is found for porous materials. In Fig. 4.6 the discrepancy between theory and practice is depicted.
Apparently, this is due to the contribution of stress-concentrations around the inhomogeneities formed by the pores. It is remarkably, that the relative strength values for metals, plaster of paris and polymers, as shown in Fig. 4.6, approximately fit the same curve.

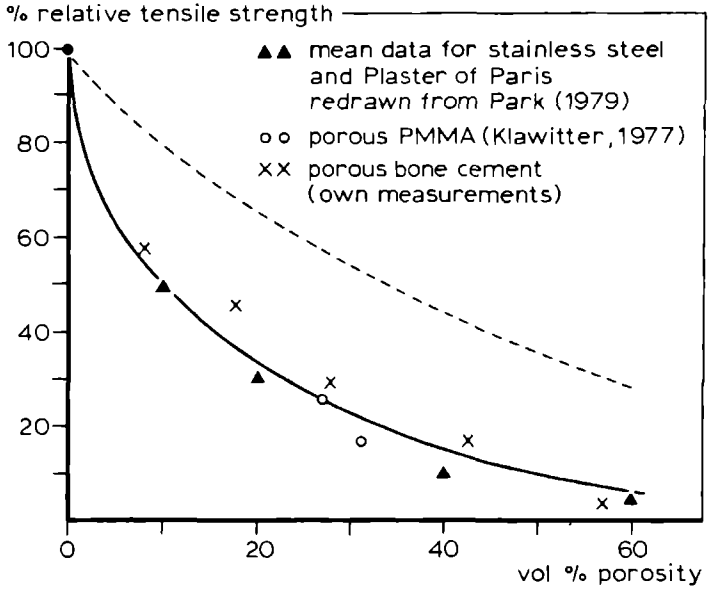


Fig. 4.6 Relative tensile strength of various materials as a function of their pore volume (the broken line represents the expression $S=S_o(1-v^{2/3})$

A first conclusion from the general picture of Fig. 4.6 could be that only basicly very strong materials - like metals and some ceramics - can be used for porous implants which are expected to be submitted to significant stresses. For instance, regular solid bone cement has a tensile strength of about 30-50 MPa and is known to be only marginal in strength when used for the purpose of cementing femoral prostheses. According to Fig. 4.6 a porous material with a pore volume of, say, 35% has lost 5 to 6 times its original strength. To replace bone cement in a femoral hiparthroplasty, a material with a "solid" strength (in tension) of 150-300 MPa would be required. However, a more sophisticated biomechanical analysis of this case should at least take into account:

- the effect of bone ingrowth, which undoubtedly will cause an altered and possibly more advantageous stress pattern in the implant
- the influence of the Youngs modulus, which is often decreased by the porosity as well.

As to this latter consideration, mention should bemade of the biomechanical analyses of Huiskes (1980). Using beams-on-elastic foundation theories and 3-dimensional finite element analysis, he derived relationships indicating that, for instance, the maximum transverse stresses in the proximal and distal region of the cement mantle in a hip arthroplastic construction are proportional to the square root of the structural stiffness of the cement mantle. This latter parameter is directly proportional to the Youngs modulus and positively correlated with the Poisson-ratio of the cement. As both the modulus of elasticity and Poisson's ratio will decrease

with increasing porosity of the cement the conclusion is that, given constant geometry and other parameters, the maximum stresses encountered in a porous cement will be lower than in a solid cement. Thus, the ratio of strength and maximum stress is less inflicted by the porosity due to the accompanying decrease of the modulus. Fig. 4.7 shows these theoretical considerations for the case of the porous bone cement using data of the tensile test (Section 4.4.2.2.) and assuming constant Poisson's ratio. The latter parameter is difficult to assess for this material but will certainly be lower due to the porosity. This will tend to further increase the discrepancy between actual strength and strength to stress ratio in Fig. 4.7. However, the decreased strength values of the porous bone cements described in the next sections cannot be reasoned away by these considerations. Especially the necessity of using porosity volumes larger than 35% - to ensure interconnectivity of the pores- means that the obtained materials are considerably less strong as compared with solid bone cements. Consequently, it is almost certain that these porous cement cannot replace solid cements in all traditional applications without special precautions.

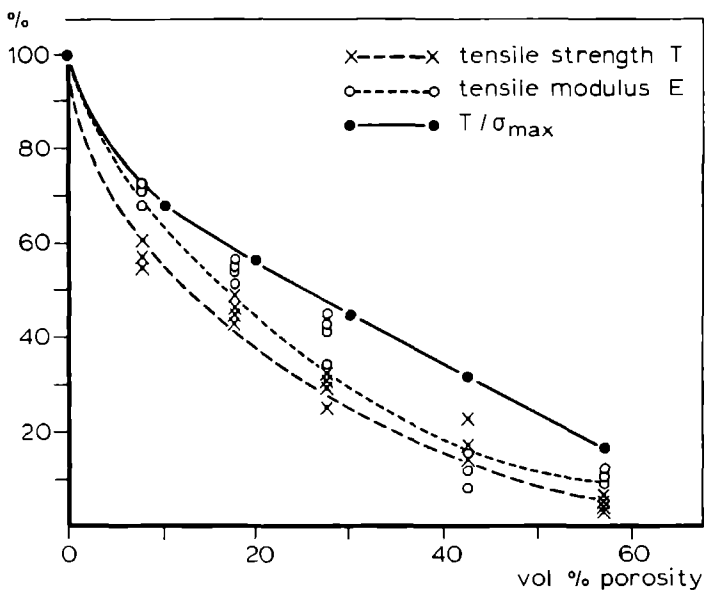


Fig. 4.7. Relative values for tensile strength (T) and Young's modulus (E) as a function of pore volume. From these values T/σ_{max} (solid line) was calculated under the assumption that σ_{max} in the cement is proportional to $\sqrt{E}$ in a hip-arthroplastic construction (Huiskes, 1980)

4.4.2. Mechanical properties of porous bone cement

In this section the porous cement is characterized as to its mechanical properties under in vitro conditions. To this purpose compression strength, tensile strength, flexural strength, impact strength as well as the moduli in compression and tension were measured as a function of pore volume and, in some cases, of pore size.

4.4.2.1. Compression test

Cylindrical specimens of 8 mm diameter and 16 mm height were prepared by curing the cement in precision-bore glass tubes. The specimens were conditioned for 24 h in water of 37° C and tested at 22° C environmental temperature on an Instron-testing-machine at strain rates of 0.001 $sec.^{-1}$.

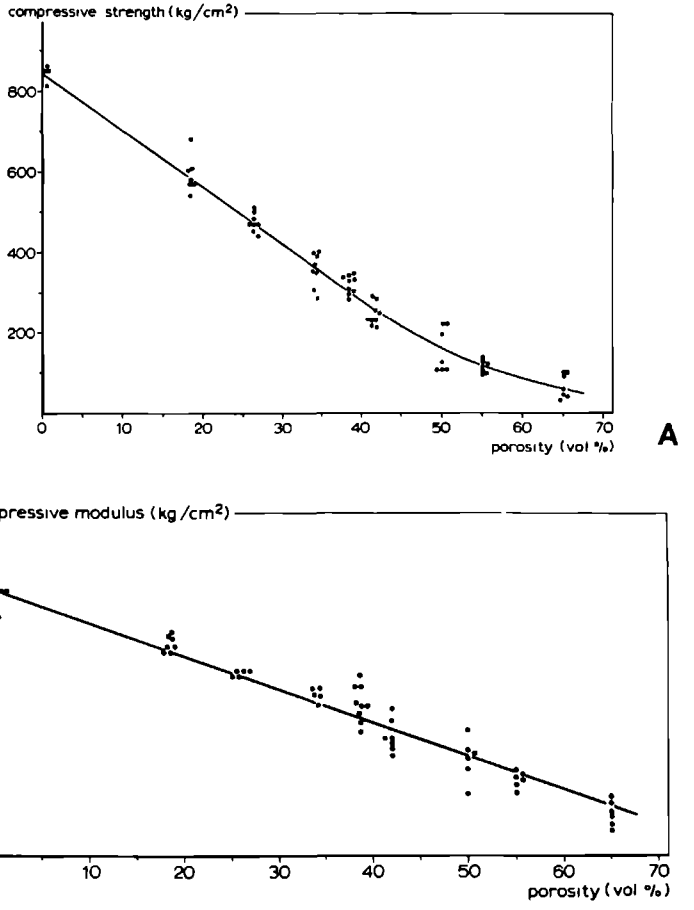


Fig. 4.8 A - B: Compressive strength (A) and compressive modulus (B) as a function of pore volume

The pore volumes were measured by quantitative microscopical analysis of polished planes cut through untested specimens. The results for the compressive yield strength and compressive modulus are given in the graphs of Fig. 4.8.A en 4.8. B.

The graph represents results obtained with samples having average pore sizes of about 600µm. These were prepared by using gels containing 7% of CMC. Experiments with other pore sizes - which were obtained by varying the powder particle size of the CMC during preparation - did not result in significant differences in the strength values. No effort was made to evaluate this parameter exhaustively, as independence of mechanical properties of pore size is a common finding for porous PMMA (Klawitter, 1977, Taylor, 1972). Very probably, the range of pore sizes relevant for biomedical purposes is much larger than the dimensions of cracks and voids that are known to determine more critically the degree of stress concentration.

4.4.2.2. Tensile test

The ultimate tensile strength of cements as a function of porosity volumes was determined by preparing rod-like specimens in glass-tubes. The diameter of the rods was 15 mm. They were fixed in the clamps of an Instron testing machine and tested at a crosshead speed of 2 cm/min. The resulting strain rate was 0.001 -0.002 sec.$^{-1}$. Only one pore size - 600 µm, as obtained with 7% CMC gel - was tested and the pore volume was varied by the relative amount of added gel. The actual pore volume was determined by using earlier obtained information about the relation between gel percentage and resulting pore volume. The results are given in Table 4.

Table 4.1. contains data also for solid bone cement, which due to monomer evaporation and air inclusions, contains about 5-7 volume percent porosity as well. The value for a truly pore-less cement was estimated on the basis of extrapolation and literature data for industrial polymethylmethacrylate (e.g. Brandrup and Immergut 1966). The latter values were used to calculate the relative strength and modulus in Fig. 4.6 and 4.7.

Table 4.1 Ultimate tensile strength and tensile modulus for cements tested at strain rates between 0.001 and 0.002 sec.$^{-1}$.

pore volume(%)	ultimate tensile strength MN/m^2	tensile modulus MN/m^2
0[1]	50	2750
7[2]	28.8 (1.2)	2020 (166)
17	23.1 (1.1)	1470 (56)
27	14.7 (1.3)	1125 (115)
42	8.3 (2.1)	323 (78)
55	2.2 (0.4)	285 (37)

Values in parentheses represent standard deviations. The number of specimens was 4-6. [1]) Estimated value for truly pore-less bone cement. [2]) Data of normal "solid" cement.

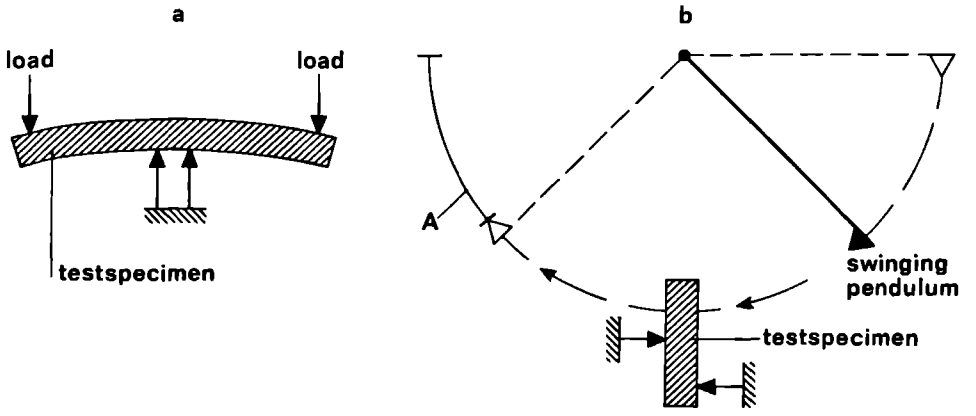


Fig. 4.9.a. The flexural test; the specimen is loaded until fracture occurs. Fig. 4.9.b.The impact strength test; the arc length A is proportional to the energy absorbed by breaking of the specimen.

4.4.2.3. Flexural strength and impact strength

For determination of the flexural strength and impact strength methods were chosen according to DIN 53452 and DIN 53453 respectively, using a Dynstat device according to DIN 51230. This method has been developed especially for the testing of polymeric materials and the use of small test specimens (15 x 10 x 2 or 3 mm). This latter feature offers good opportunities for working with specimens obtained from in vivo experiments (See chapter 6). The schemes of these tests are given in Fig.4.9. In Fig. 4.10 the Dynstat device and details of the construction are shown.

Table 4.2. Flexural strength and impact strength.

pore size	pore volume (%)	flexural strength MN/m^2	impact strength $KN\ m/m^2$
-	0	81.4 (4.2)	6.2 (0.62)
small	42	18.4 (0.9)	1.2 (0.15)
small	55	7.5 (0.8)	0.75(0.05)
large	42	18.7 (0.1)	1.34(0.04)
large	55	6.7 (0.1)	1.0 (0.01)

Values in parentheses are 95% confidence intervals of the mean.

Specimens were obtained from plate material (cement cured between glass plates) by machining and grinding to the desired dimensions. Cements to which 35 and 50% gel had been added were used and this resulted in porosities of 42 and 55% respectively. The pore size was varied to some extent by preparing the cements by using "small" (< 125 μm) or "large" (~ 700 μm) grain-size CMC powder.
Table 4.2. summarizes the results. It appears that the values are severely decreased in comparison with solid (0% porosity) cement. Again the relative insensitivity of the strength values for the size of the pores is demonstrated.

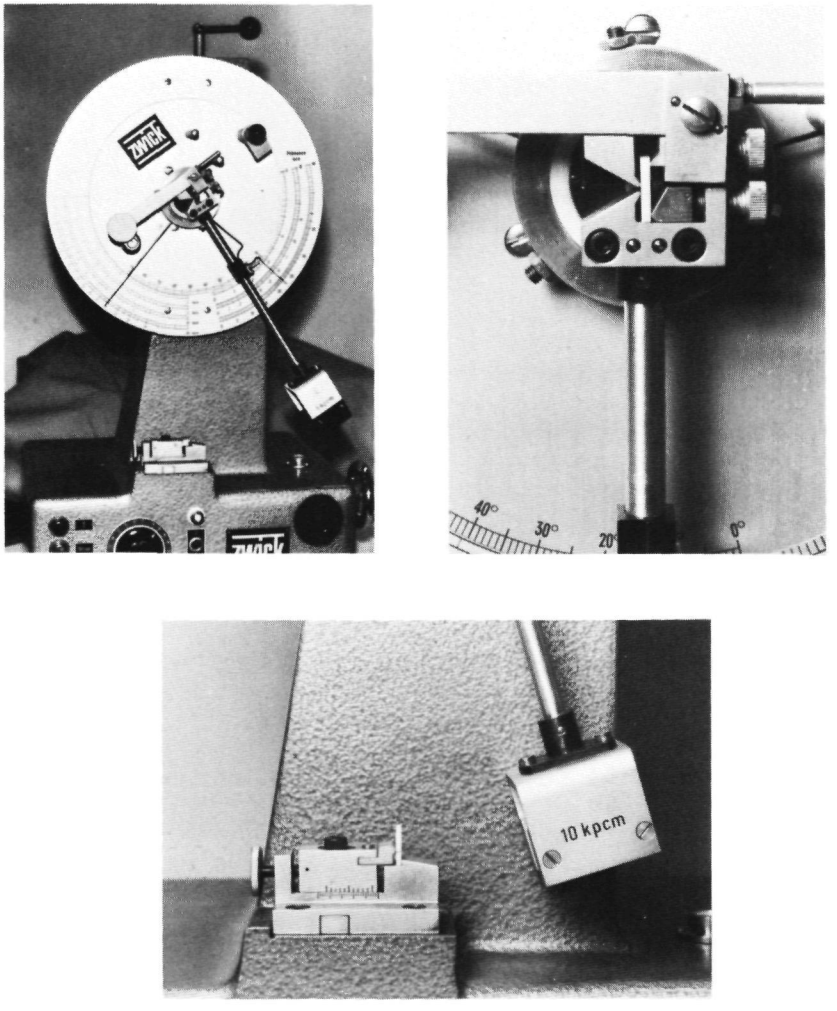


Fig. 4.10 The Dynstat device (top left) and details of fixture for the flexural test (top right) and the impact test (bottom).

5.1. Experiments in the cancellous bone of the forehead of swine*

5.1.1. Choice of the experimental animal and the implant site

The reactions of living tissue to implanted materials depend strongly on a large amount of variables and conditions. The chemical composition of the implant material, the shape of the implant, the loading condition of the implant construction are only a few examples of the variables, each of which can decisively influence the response of the host tissue.
Consequently, the evaluation of the biological response of a relatively new implant material requires a large amount of in vivo experiments before a satisfactory knowledge of the biological properties of the material is obtained. Therefore such an evaluation will be promoted by the choice of an experimental biological environment from which a quick response can be expected. In addition, care must be taken that the biological system is not disturbed too much by the implantation per se, in other words, that the dimensions of the implantation site are relatively large with respect to the dimensions of the implant. Moreover, a large implantation area offers the possibility for placing more implants with different properties in the same animal, thus excluding inter-animal differences at least to some extent.

As in the case of the gel cement the interest is primarily directed to its capabilities for fixation, thus to the reaction of bone tissue, the above mentioned considerations led to the selection of cancellous bone as biological system; a much quicker response of this, well vascularized, tissue can be expected as compared to cortical bone. A comparison of readily available experimental animals learned that the forehead (os parietale and os frontale) of the swine (Sus scrofa) offers a very well accessible, large implantation area consisting of enough spongious bone to incorporate several implants (Fig. 5.1).

5.1.2. Test variables

Important variables of the gel cement with regard to biocompatibility and tissue ingrowth can be expected to be:

*This study was done under the supervision of Dr.P.J. van Mullem, Dept. of Oral Histology of the University of Nijmegen (Van Mullem et al. 1978, 1980).

- the pore size
- the concentration of CMC in the aqueous phase
- the presence or absence of monomer

As explained in section 3.4 the first two variables are interrelated: a low CMC concentration (low gel viscosity) results in a cement with large pores, whereas a high CMC concentration results in a cement with small pores. The contamination of the biological environment of the implant with monomer can be controlled to some extent by curing the implants in situ or by implanting prepolymerized specimens.

In order to differentiate between the influence of these variables on tissue reactions, cements with two levels of pore sizes were selected for implantation: small pore cements (S) in which the average pore size was about 100 µm (CMC concentration 20%) and large pore cements (L) with an average pore size of about 700 µm (CMC concentration 7%).

Both levels of pore sizes were realized in prepolymerized (PP) implants and in situ curing (ISC) formulations. Additionally, advantage was taken of the possibility offered by the prepolymerized implants to remove the original gel phase (by washing with distilled water) and to replace it by gels of other concentrations or saline solution (by impregnation with the specific solution).

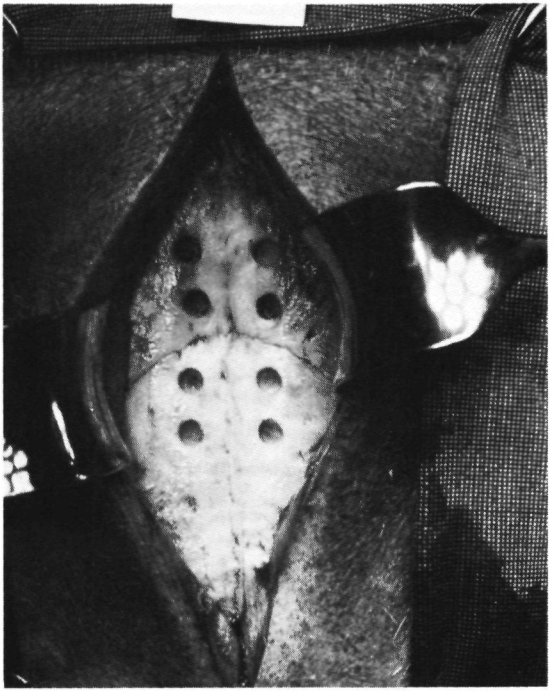


Fig.5.1.A. Operating field demonstrating both osses parietale above the horizontal arch-like suture and both osses frontale below the suture. This swine provided eight sites of implantation.

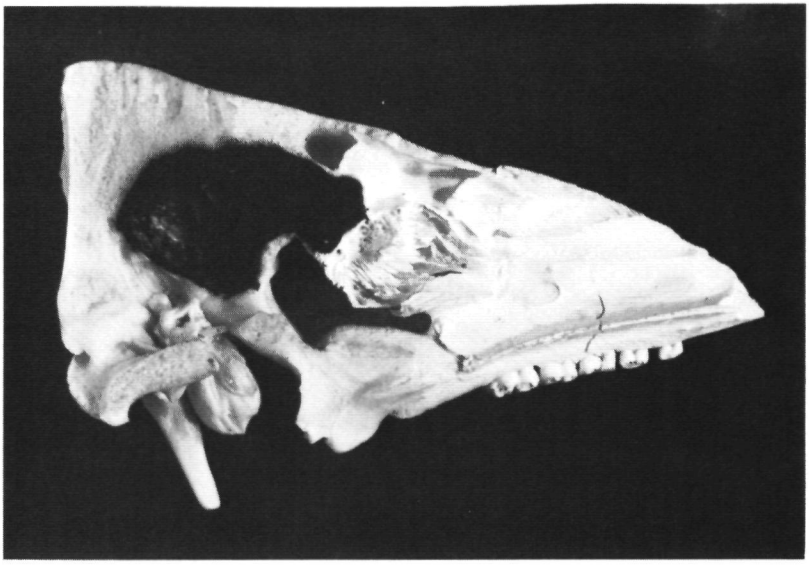


Fig. 5.1. B Cross section through the skull of a swine demonstrating large quantities of bone especially in the os parietale.

A solid cement (C) was also included for the purpose of comparison. Table 5.1 summarizes the various cements which all were obtained and prepared under sterile conditions.

Table 5.1

Description of the implanted cements

Code	Curing condition	Pore size	CMC*conc. of aqueous phase
PP-S-7	prepolymerized	100 µm	7%
PP-S-0	prepolymerized	100 µm	0% (saline)
PP-L-20	prepolymerized	700 µm	reimpregn. with 20%
PP-L-7	prepolymerized	700 µm	7%
PP-L-0	prepolymerized	700 µm	0% (saline)
ISC-S-20	in situ cured	100 µm	20%
ISC-L-7	in situ cured	700 µm	7%
ISC-L-7p	in situ cured	700 µm	7% (purified CMC)
C	in situ cured	solid	-

*Nymcell, ZHF 50, Nyma, the Netherlands

5.1.3. Operation procedure and histological processing

The experimental animals were 6-8 month old swine (Sus scrofa) weighing 80-120 kg. Before operation, the animals were anaesthesized using 2 mg/kg Stresnil and 0.1 mg/kg atropine given intramuscularly, after which 20 mg/kg Nembutal was given intravenously. The operation was performed under intubation using N_2O + O_2 + Fluothane. Normal antiseptic procedures and precautions belonged to the routine of the operating room.
A median incision was made in the skin starting at the os occipitale. After lifting of the periost, the implantation area - os frontale and os parietale - was recognizable by the pattern of the sutures in the skull. On both sides of the median suture, 4 or 5 cavities were drilled: 2 in the os parietale and 2 or 3 in the os frontale (Fig.5.1.A). The cavities measured 5-7 mm in diameter and were drilled to a depth of 5-10 mm using an air-driven trephan. During drilling, cooling was accomplished by spraying with copious amounts of physiological saline solution. Before placing the implants, bleeding was controlled and the cavities were dried with cotton gauze. After implantation, the periost was replaced and sutured over the implants. The sutured wounds healed without complications within 10 days, the risk of wound infection being diminished by administering antibiotics during the first week postoperatively. No bone labelling agents were applied in these experiments.

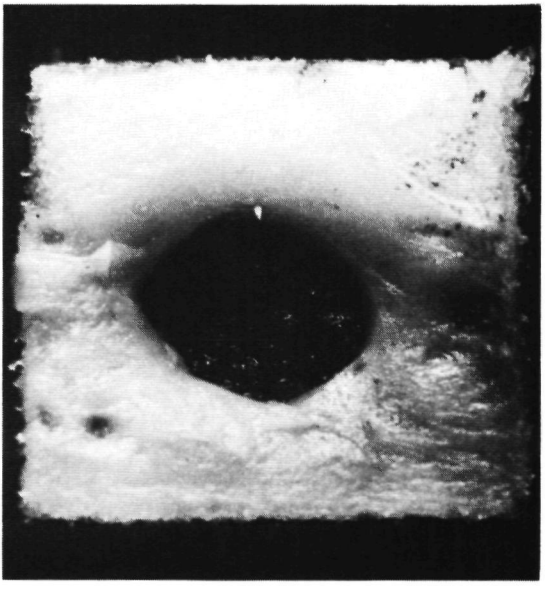


Fig. 5.2. Macrophotograph of a block of bone containing a 10 week old implant, the dorsal aspect of which is going to be overgrown with bone.

After sacrifice - anaesthesia followed by cardiac puncture - blocks of tissue containing the implants were sawn out with a bandsaw and fixed immediately by immersion in a 4% neutral formaldehyde solution. The obtained blocks (Fig. 5.2) were decalcified in 5% formic acid and embedded in an embedding medium based on glycolmethacrylate (JB4, Polysciences Inc., U.S.A.). 7 µm thick sections were cut and each 25 th section was haematoxylin (Harris) - toluidin blue - acid fuchsin stained.
The glycolmethacrylate embedding medium was chosen in order to preserve the integrity and coherence of the hard tissue, the soft tissue and the PMMA implant material.
Sectioning blocks containing hard tissues as well as implant material and having a size of about 1 x 1 x 1 cm, storage and staining of the sections required extensive experimentation before the technique could be applied routinely.
The sections were blindly evaluated using normal microscopical techniques.

5.1.4. Histological parameters

The material obtained was examined histologically for:
1. the tissues immediately surrounding the implant - the "peri-implant" area - and
2. the tissues that had grown into the pores of the cement.

Attention was directed to the following phenomena:
- Necrosis and bone resorption in the peri-implant area.

The influence of the preparation of a cavity in the bone as well as a possible noxious influence of the implanted material can vary from nil to some degree of necrosis of the hard tissue surrounding the implant. In the latter case the reaction of the body might consist of resorption of the necrotic material by osteoclasts. This mechanism may result - at least initially - in a gap between implanted material and remaining hard tissue (Fig. 5.3).

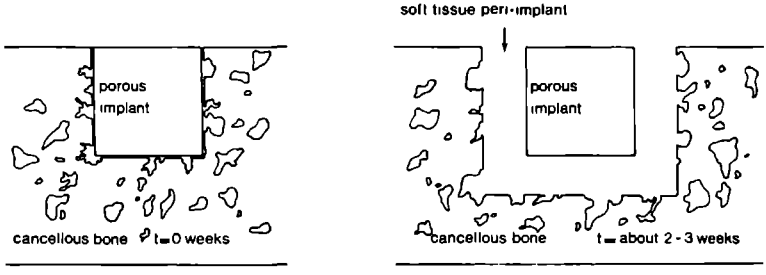


Fig.5.3. Schematic drawing of the formation of a gap between the implant and the surrounding bone.

This interphase will be filled up with (inflamed) soft connective tissue (Figs. 5.4 and 5.5).

- The width of the connective tissue gap mentioned above can be considered as a measure for the severity of the reaction.
- Inflammatory tissue around and in the implant.

The presence of a vascular type of inflammatory reaction reflects the reaction of the body to dispose of toxic substances and/or damaged tissue material (Fig. 5.6). Consequently, inflammation can occur in the peri-implant area as well as in the tissues that have invaded the pores of the implant; around the implant on the basis of both of the tissue inflictions mentioned above, and in the implant because of any noxious substance originating from the implant material. The amount of inflammatory tissue observed can be considered as a measure for bio-incompatibility.

- Layer of condensed bone around the implant

When the implant has been accepted by the body, new bone is deposited on existing trabeculae and is formed in the gap that resulted from the initial resorption process. In cancellous bone this bony layer is marked by its compact appearance (Fig. 5.7).

- Necrotic tissue in the pores of the cement.

Tissue that obviously invaded the pores of the cement initially, sometimes appears to necrotize afterwards (Fig. 5.6).

- Ingrown bone

When bone grows into the pores of the implant, it not only reflects the body's acceptance of the material but also the readiness of the body to restore the initial situation, using the pores of the implant to locate the bony trabeculae. Invasion of the implant by sound mineralized tissue provides the desired situation: the implant is fixed to the bone (Figs. 5.8 and 5.9).

Thus, having in mind the histological criteria mentioned above, a favourable final situation is attained when:

- no necrosis or inflammatory reactions are present in and around the implant.
- no connective tissue interphase of any appreciable extent is present between that part of the implant surface which consists of PMMA polymer and the surrounding bone;
- a layer of compact bone surrounds the implant;
- bone ingrowth has taken place in a sufficient number of pores to establish fixation of the implant.

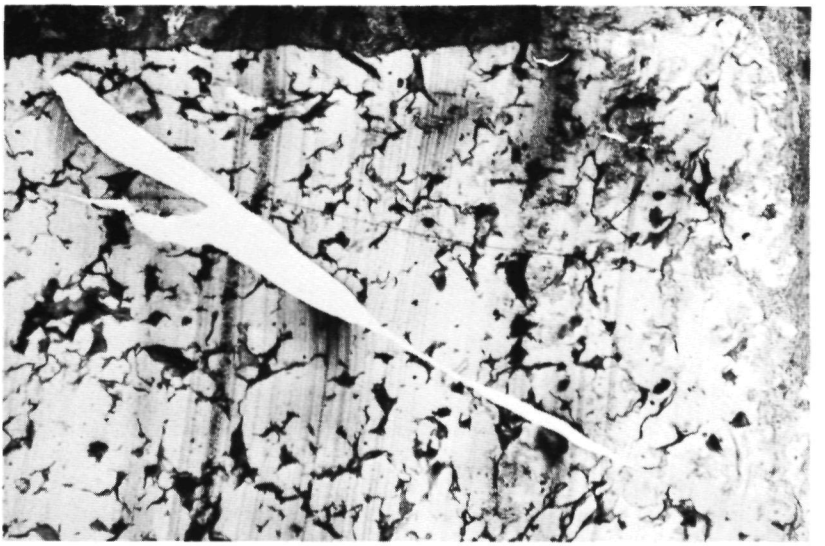


Fig. 5.4. The very beginning of peri-implant gap formation. At the top right corner of the implant bone is being resorbed.

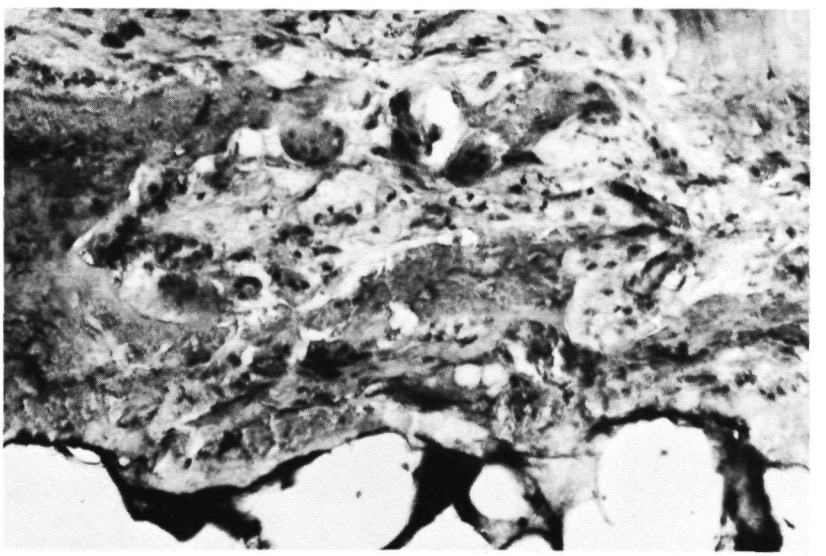


Fig. 5.5. Osteoclasts resorbing necrotized bone adjacent to the implant (*bottom*) thus creating an interphase.

Fig. 5.6. Part of an implant and its interphase. The interphase demonstrates a severe inflammatory reaction. In most of the pores necrotic (soft) tissue is present.

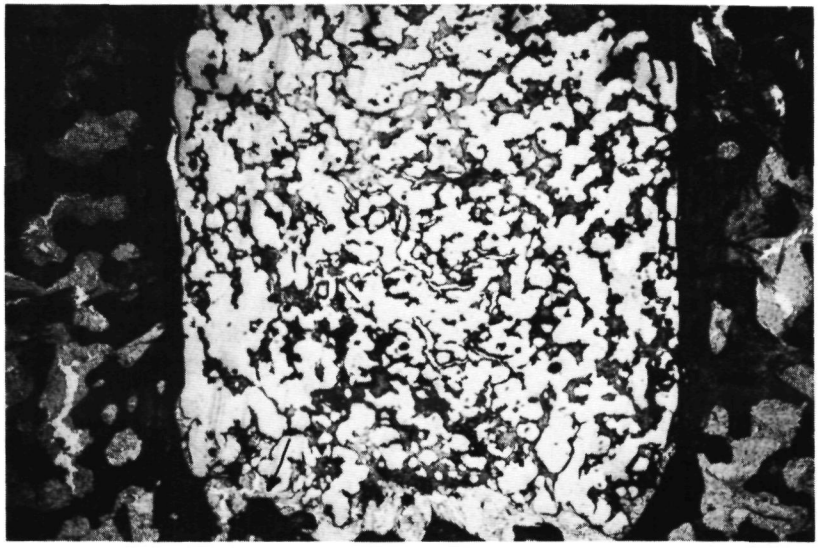


Fig. 5.7. Layer of condensed bone around a small pore implant. No bone ingrowth into the pores, except in an accidentally large, superficial, pore (arrow).

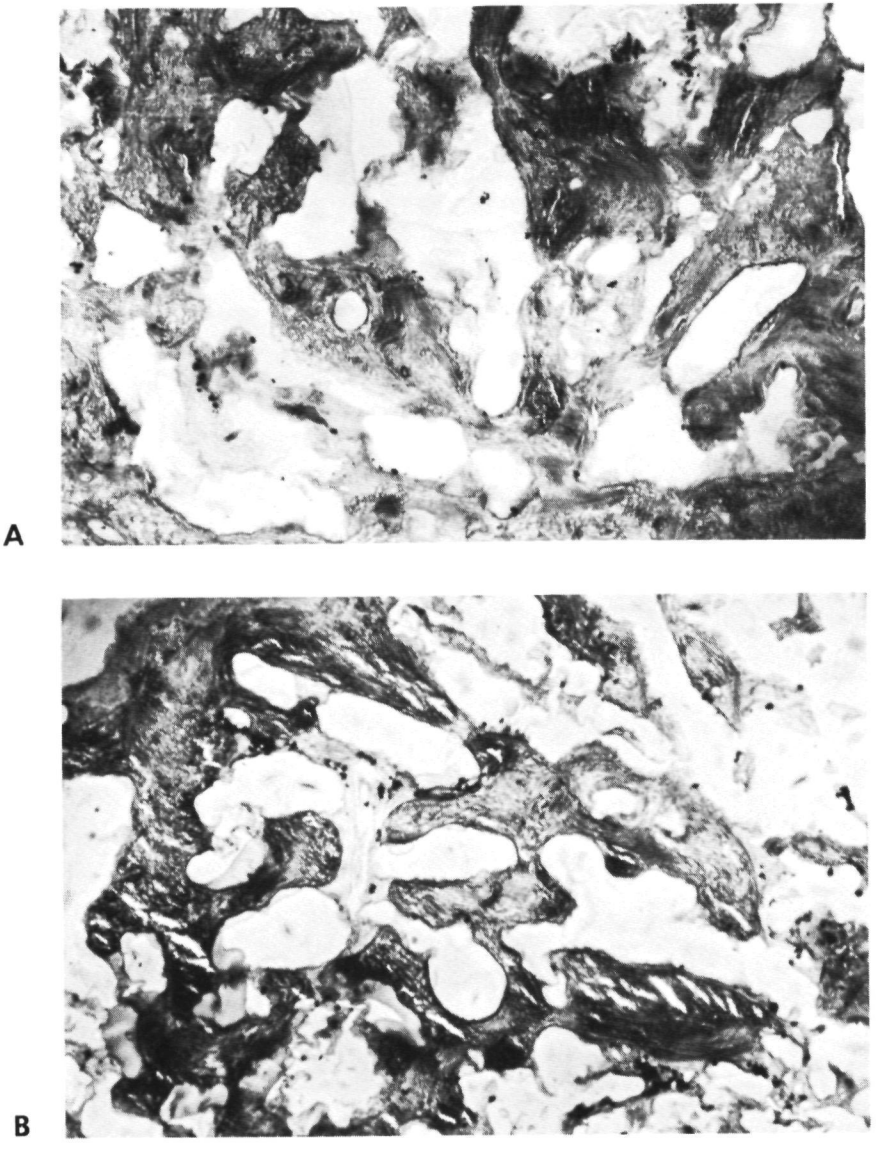


Fig. 5.8 Low power photomicrographs of a corner (A) and the centre (B) of a 26-week implant demonstrating large amounts of bone in the pores.
A. bone dark grey, soft tissue light gr , nuclei unstained, zirconium oxide black PMMA white.
B. haematoxylin-toluidin blue acid fuchsin staining.
In both micrographs, masses of zirconium oxide (black) are found in the soft tissues.

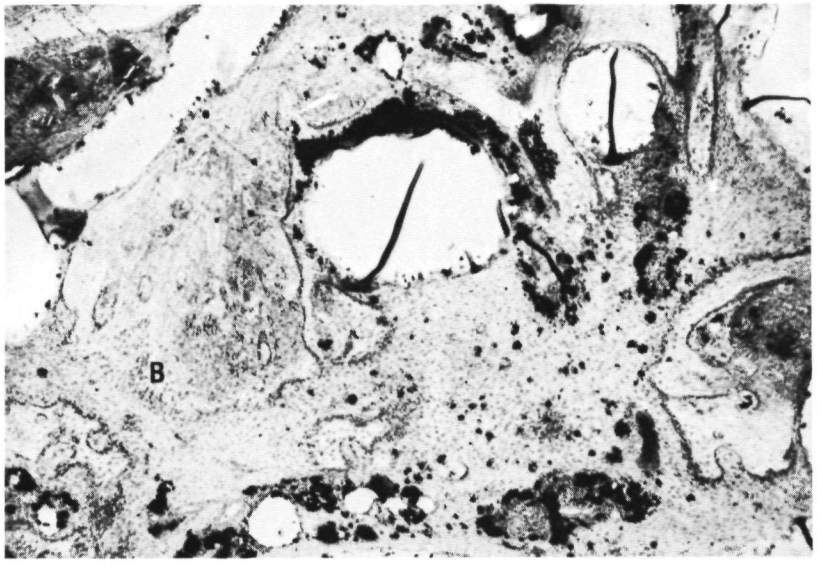


Fig. 5.9 High power photomicrograph of the centre of a 26-week implant demonstrating recently deposited bone (B) and soft tissue containing aggregates of coarse granular zirconium oxide (black).

5.1.5. Results

5.1.5.1. The peri-implant area

In the next tables (5.2-5.4), the discussed phenomena are presented as a function of the type of cement and of the experimental period. In the tables, a double drawn line indicates the period after which the phenomenon has come to what is regarded as the favourable final situation. At first glance, the data in the tables 5.2-5.4 seem to lead to the following conclusion: with respect to the width of the peri-implant gap and the layer of condensed bone the most adverse reactions (varying from multiple inflammatory foci to nearly generalized inflammations) and the consequent long time before the desired final situation is attained, are encountered in the cases of small pores and/or the highest CMC concentrations (20%).

It appears that the body has equal difficulties in attaining the favourable end situation using ISC-S-20 or PP-S-0 implants. This indicates a relative independency of the CMC concentration. Regarding pore size, PP-L-0 implants, which differ from PP-S-0 implants in pore size only, reach the favourable end situation in shorter time. The best results are obtained with ISC-L-7 implants, all adverse reactions having subsided within 6 weeks, despite of the higher CMC concentrations in comparison with PP-L-0 and PP-S-0 implants.

A more detailed consideration of the differences in the tissue reactions to the various types of implants has to include the

implant's "history". The implants do not only differ in pore size and actual concentration of CMC in the pores, but also in the time during which they had been in contact with gels of different CMC concentrations. This contact had taken place during the period between preparation of the implant and the actual implantation. Thus, the following "histories" existed:

- PP-S-7 implants had been prepolymerized using 20% CMC gel. This gel was washed out and the implants were then reimpregnated with 7% gel by immersion in an excess of 7% gel for at least 10 days.
- PP-S-0 as well as PP-L-0 implants were prepared using 20% and 7% gels resp. to create the pores. The gels were then washed out with sterile physiological saline solution, in which the specimens were preserved until the time of operation.
- PP-L-7, PP-S-0 and PP-L-20 implants were prepared using 7% or 20% gels, to create the pores, and were preserved in excess of 7% or 20% gels resp. until the time of operation.
- The other implants, ISC-L-7 and ISC-S-20, had been in contact only with the very small amount of gel that is actually present in the pores, because these formulations were prepared immediately prior to operation.

Table 5.2.
Width of peri-implant gap (µm).

EXP. PERIOD (wks.)	CEMENT								
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p	C
1									0-800
3	0-500	50-800	0-900	150-400	0-1100	150-600	0 0-950	0-100 0-150 0-400	0 0-300
6	0-600	0-120 0	300	0-450 0	0-150 0-100	0-250 0-150 0	0 0 0	0	0-50
10	0-300	0 0-100	400 0-350	0 0	0 0	0 0	0 0 0		
15	0 0	0 0	0 0	0 0			0 0		
26							0 0		

When it is assumed that the CMC compound, which was used "as received" in these experiments, contains a noxious substance, the observed sequence of decreasing tissue reactions (Tables 5.2, 5.3 and 5.4) can be explained consistently. The small pore implants either contain large amounts of CMC (20%, as is the case in PP-L-20) or have been prepared with 20% CMC and have been in contact with lower CMC-concentrations for longer time. Both, during the mixing of the cement and during the contact-time, noxious substances could have been absorbed in the polymer phase. This could explain the relatively small differences in tissue reactions provoked by the ISC-S-20, PP-S-7, PP-S-0 and PP-L-20 (the first four listed in the tables) implants.

Table 5.3

Inflammatory Tissue in the Peri-implant Area.

EXP. PERIOD (wks.)	CEMENT								
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p	C
1									+
3	+	++	++	++	++	++	+ +	- + ±	+ - -
6	++	± - -	++	+	±	+ + -	- -	- -	
10	+	+ +	++ ++	+ +	- -	- -	- -		
15	- -	- -	- -	- -	- -	- -	- -		
26							- -		

- no reaction
± one focus or one coherent area of inflammatory cells in the sample series of sections.
+ two or more foci or areas, but not a (nearly) generalized inflammatory reaction.
++ (nearly) generalized inflammatory reaction.

The much better compatibility of ISC-L-7 when compared with PP-S-7 implants, which was unexpected as mentioned above, can now be explained on the basis of absorption of a noxious substance during the long contact-time in the case of the PP-S-7 implants. The solid implants (C) did not give better responses than the large pore cements and had not been in contact with the gels at all.

Table 5.4

Layer of Condensed Bone around Implant

EXP.. PERIOD (wks.)	CEMENT								
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p	C
1									-
3	-	-	-	-	-	-	-	- - -	- -
6	-	± +		- +	- -	+ +	+ +	+	±
10	+	+ +	- -	+ +	+ +	+ +	+ +		
15	+ +	+	+	+	+	+	+		
26							+ +		

- lamina dura not present
± at one side of the longitudinally sectioned implant
+ at two or more sides

5.1.5.2. Tissue reactions inside the implant

Roughly the same phenomena were observed in the tissues in the pores of the implant. The tables 5.5 and 5.6 list the rate at which inflammation and necrosis were provoked and subsided in the various implant types. The scores for bone ingrowth into the pores of the cements are given in table 5.7.

Only in the case of ISC-S-20 a substantial amount of CMC was still present in the pores after 3 weeks. Apparently, the pores of all other implants were invaded by soft tissue in a very short time and to the expense of the CMC gel initially present.

Especially in the case of the small pore cements, the invaded tissue, besides showing inflammation, demonstrated necrosis (tables 5.5 and 5.6). Necrosis may have been due either to the small diameter of the pores which appeared to restrict the ingrowth of blood-vessels - thus depriving centrally located cells of oxygen - or by the presence of CMC which is suspected to contain the noxious compound. In addition, the noxious compound could have been diffusing out of the polymer phase.

Table 5.5.

Inflammatory Tissue in Implant Pores.

EXP. PERIOD (wks.)	CEMENT							
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p
3	+	+	-	++	+	++	++	±
6	+ +	+ ±	+	- ±	+ -	+ + -	- +	-
10	+	+ -	+ +	+ ±	+ -	+ -	+ -	-
15	- -	± ±	- -	- -	- -	+ ±	- -	
26							- -	

- no reaction
± one focus or one coherent area of inflammatory cells in the sample series of sections
+ two or more foci or areas, but not a (nearly) generalised inflammatory reaction
++ (nearly) generalised inflammatory reaction

In the large pore cements necrosis was almost or completely absent. Bloodvessels appeared to grow into the large pores in shorter time. Obviously,the pore surface is much smaller than in the case of small pore cements and this may have confined the diffusion of the possible noxious compound from the polymer phase.
Inflammation appeared to be quite independent of the CMC concentration and was similar in large or small pore cements. Ingrowth of bone (Table 5.7) was not observed in small pore cements. Large pore cements allowed for bone ingrowth but here a distinct CMC effect could be determined; a high CMC concentration resulted in a lower ingrowth rate.

Table 5.6

Necrotic Tissue in Implant Pores

EXP. PERIOD (wks.)	CEMENT							
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p
3	++	+	++	+	±	-	-	-
6	+	+ +	+	- ±	- -	- -	± -	-
10	+	± -	+ ±	- ±	± ±	- -	- -	
15	- ±	- -	- -	- -	- ±	- -	- -	
26							± -	

- no necrosis present
± small scattered areas of necrosis
+ larger mass of necrotic tissue
++(nearly) generalized necrosis

Consequently, it is our conclusion that:
1) the large pore cements appear the most favourable with regard to the ingrowth of bloodvessels and bone,
2) the CMC powder as received is suspected to contain a compound which is responsible for retarding the attainment of a favourable end situation.

At this stage,it was decided to focus further attention to large pore cements and low CMC concentrations because of the desirability to have implants which allow for rapid tissue ingrowth.

After the suspicion of a noxious contaminant in the CMC powder had risen, the as received powder was subjected to Soxhlet extraction with 96% ethanol. After 48 hrs., the extract contained 1.5-1.8% (relative to dry powder) of a yellowish, readily water soluble compound. The extract was suspected to contain appreciable amounts of iron - as most technical CMC's can contain up to several hundreds of ppm of it - but this could not be confirmed by UV spectrophotometric analysis. The other possibility is that low molecular weight CMC and/or sodium glycolate are major components of the extract. No effort was done to establish the exact composition of the extract.

In further experiments CMC, purified as described above and polymer powder without ZrO_2, was used.

Table 5.7

Ingrown Bone

EXP. PERIOD (wks.)	CEMENT							
	ISCS20	PPS7	PPS0	PPL20	PPL7	PPL0	ISCL7	ISCL7p
3	-	-	-	-	-	-	±	+ + +
6	- ±*	- -	-	+ +	- +	+ + +	+ ++	++
10	-	- -	- -	± ++	++ ++	++ ++	++ ++	
15	- ±*	- -	- -	+ ++	+++ +++	++ ++	+++ +++	
26							+++ +++	

- no bone ingrowth *: incidently in large peripheral pores
± initial stage of ingrowth at one or two sites at the perifery of the implant
+ initial stage of ingrowth at more than two sites in the sample series of sections
++ ingrowth further advanced than +, but less than 50% of the volume of the pores of the implant is filled with bone
+++ more than 50% of the volume of the pores is filled with bone.

Tables 5.2 - 5.7 show the results obtained with in situ cured large pore cements in the column ISC-L-7p. The advantageous effect of the purification is reflected by the scores in the tables. Better

results were obtained in comparison with PP-L-7 and ISC-L-7 implants in many aspects. For example, using ISC-L-7p cement bone ingrowth after 3 weeks is of the same extent as is found in the most favourable type of the other implants only after 6 weeks. Moreover, CMC gel remnants were observed in the implants with unpurified CMC even after 26 weeks, whereas they were almost completely absent after 6 weeks in the case of purified CMC. Even resorption of bone that had been necrotized during the drilling of the cavity did not hinder the body to start ingrowth of tissue immediately. Obviously, the removal of a noxious substance from the CMC enables the body to this prompt start of tissue reactions leading to the desired final situation. Summarizing the above discussed results it can be concluded that:

- small pore cements, obtained with high concentrations of CMC in the aqueous phase, give rise to prolonged inflammatory and necrotic reactions. As such, these cements are unacceptable for implantation in the human body. Notwithstanding these prolonged reactions,a sound situation is attained after about 15 weeks; bone ingrowth, however, does not take place.
- Cements with pores in the range of 350 - 1000 μm which are obtained with 7% purified CMC in the aqueous phase, provide a favourable outlook for orthopedic, dental and surgical application in humans, as far as biocompatibility is concerned. Necrosis in or around the implant does not take place.
  Inflammation subsides within 3 weeks. Bone ingrowth is substantial after 6 weeks. A layer of condensed bone is deposited around and in close contact with the implant.
- In all further experiments,ISC-L-7p type of cement should be the material of choice.

5.2. Results of other experiments

In this section,summaries will be given of work which has been done by Ypma (1979,1981) and Vaandrager (1980,1981) and which contributes to the understanding of the biocompatibility of the porous cement. The work of Ypma concerns an investigation to the possibility of using the porous cement as an anchoring medium for total hip prostheses and consists essentially of two parts: an evaluation of histological responses of the femoral and acetabular bone of sheep to the cements,when used in a loaded situation,and a biomechanical investigation to the mechanical performance of the porous cements in this application.
The results of the first mentioned part will be summarized in section 5.2.1.
Vaandrager, working at the department of plastic surgery of the University of Rotterdam, explored the gel cement for its use as a material for cranial augmentations and for repair of cranial defects in an experiment with monkeys. Section 5.2.2. will give the highlights of his results as to biocompatibility of the cement and bone ingrowth. The histological evaluation was performed by van Mullem (1980, 1981A).

5.2.1. Gel-cement as an anchoring medium for total hip prostheses.

As one of the important purposes of the study of Ypma (1981) was to detect whether the porous cement is able to withstand the stresses as encountered in a human total hip arthroplasty, the sheep was chosen as an animal model. By its anatomy and body weight (60-80kg), this animal provides a very representative model of the human hip, as far as the stress pattern is concerned (Bergmann et al. 1980). Studies as described in section 5.1 had learned that only the use of large pore cements was sensible, so large pore (7% CMC) cements were used with pore volumes of 35% (the lower limit for interconnection of pores) and 50% (the upper limit for residual strength). Normal solid bone cement was included in the experiment to provide an opportunity to compare the weaker cements with a material that has proven to be strong enough for the purpose. To exclude effects due to operational trauma and other systematical error sources, a number of animals were treated by filling up the medullary cavity with gel cement, leaving the joint itself intact.
Since it was expected that the weakest cement (50% pore volume would not withstand the stresses at the interface of prosthesis stem and cement, a series was included in which te stem of the prosthesis was precoated with a layer of solid cement. These coated prostheses were cemented in the femur using 50% porous cement, thus providing a situation in which the strong, solid cement was used in the region of the highest stresses and the possibility of fixation by bone growth into the porous outer layer was maintained.

Totally, 33 animals were used; experimental period were 6 weeks, 3 months, 6 months and 12 months. The prosthesis that was used was designed for large dogs (Protusal^{R}, Sulzer, Winterthur, Switzerland) but appeared to be suitable for sheep as well. The acetabular cup was made of ultra high molecular weight polyethylene (Sulzer). After sacrifice of the animals, the obtained material was, inter alea, studied macroscopically for ectopic calcification and microscopically for bone ingrowth, fibrous tissue density, fibrous tissue necrosis, inflammatory cells, cortical bone necrosis and cortical cancellation, being the main histological parameters defining the tissue reactions to the implanted cement.

The results indicated that none of the sheep treated with porous bone cement showed untoward tissue reactions. All porous cement groups differed essentially from the animal treated with solid cement with respect to the phenomena at the bone-cement interface.
The peri-implant fibrous tissue membrane, which was always found to encapsulate solid cement implants, was absent in the case of porous cement. The foreign body giant cells and macrophages observed at the bone-cement interface in the case of solid cement were not seen with porous cement. Bone ingrowth was observed to start after 6 weeks and to be in progress after 3 months; further maturation and stabilization of the calcified tissue occurred at 6 months and 1 year. The depth of ingrowth averaged 2 mm and did not

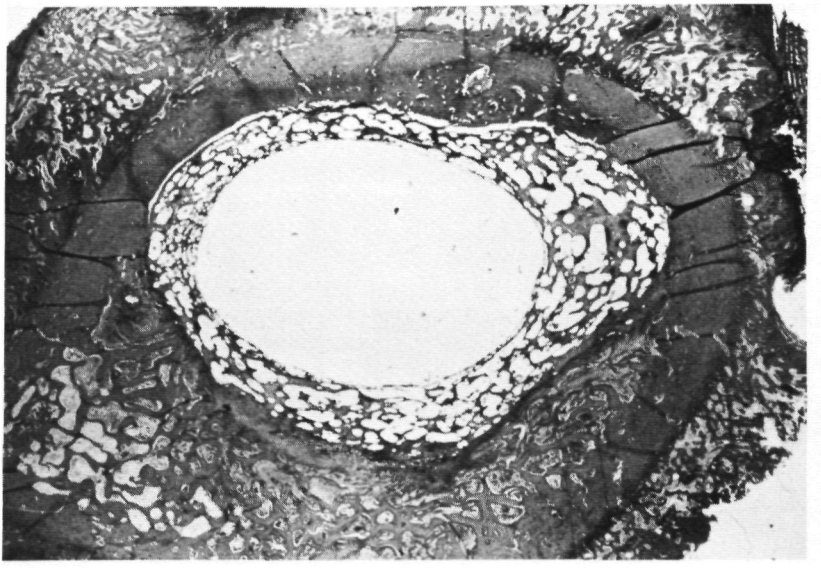


Fig. 5.10 Cross section through a femur 6 weeks after operation. The pores of the cement are filled with healthy connective tissues.

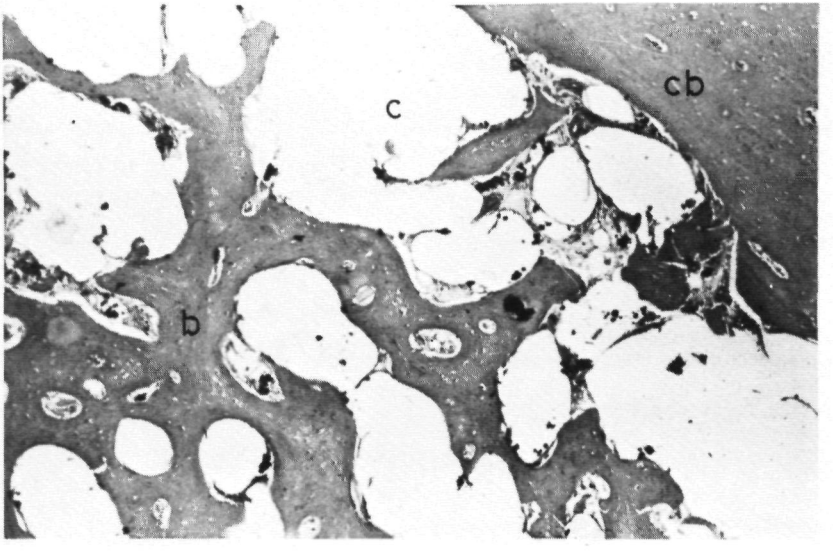


Fig. 5.11 Detail of the ingrown tissue after 3 months.Note close adaptation of cortical (cb) and ingrown bone (b) to the cement (c).

depend on the volume of the porosity. At the sites where the cement had been heavily loaded, bone ingrowth lagged behind - as was the case proximally, under the collar of the prosthesis - or was absent at all as was observed around the prosthesis stem where the stresses are highest. The fact that in these areas the vascular system may have been more severely damaged or can less easily be restored by the body, should also be taken into account, however.

The different types of cement proved not to differ in degree of provoked cortical necrosis and in all cases a time dependent restoration of cortical vitality was observed. Fig. 5.10 and 5.11 give some examples of the favourable situation in and around the porous cement. These findings are consistent with the ingrowth rates and tissue reactions in the swine experiments as described in section 5.1.

Especially where cortical necrosis is concerned, the results of Ypma are not consistent with those of Feith(1976), who found a much milder reaction to the porous cement in comparison with solid cement when implanted in the femora of rabbits. The Ypma study does not discern a difference between solid and porous cement in this respect.

The problems which were encountered with the use of porous cement in the specific application of hiparthroplasty seem all to be related to the low strength of the material. Ypma concluded that the porous cement was biocompatible and allowed for porous attachment but should be sufficiently strong to withstand the stresses which can be expected.

5.2.2. Porous cement as a material for augmentation of cranial deformities and repair of cranial defects

Acrylic resin, either in the form of in situ curing solid bone cement or of a prefabricated appliance, has been used extensively in corrective and reconstructive surgery (See Table 1.1). In spite of the good biocompatibility and processability of the material - which have led to many succesfull applications - stable attachment of the solid implants to bone is not obtained without special precautions. Actually, these solid implants invariably become surrounded by a thin connective tissue membrane. The porous acrylic cement with its features of porous attachment and capability of being processed in the mouldable state, holds a promise for valuable improvements of some surgical reconstructions. One of the frequently occurring tasks of the plastic surgeon is the correction of cranial assymetries by augmentation. Up to now, most of these assymetries are corrected by bone transplants or appliance of preshaped prostheses. Another problem which often occurs, is the repair of cranial defects, where large quantities of bone have gone lost by trauma of pathological causes. Again, a cement which can be shaped and formed in situ and allows for fixation by bone ingrowth, could be an attractive alternative for bone transplants - offering the risk of renewed resorption - or alloplastic inserts which never become really attached to the margins of the defect.
To explore the possibilities of the porous cements in these appli-

cations, Vaandrager et al.(1980)and van Mullem et al. (1980, 1981A) performed an animal experiment in which two augmentations were placed on both osses parietale of the skull of monkeys (Macaca speciosa). The augmentations had the form of a spherical segment measuring about 25 mm in diameter and 5-7 mm in height. The used cement was prepared with 7% CMC-gel (pore size 700 µm),the pore volume being 50%. Treatment variables consisted in the absence or presence of the tabula externa (cortical bone)in the area of the skull where the augmentation was placed on. After the experimental period - extending to 52 weeks - the augmentation was harvested together with the underlying bone as a biopt, leaving a circular defect in the monkey's skull. This defect,exposing the dura mater, was instantaneously filled up with the same cement and was allowed to harden in contact with the dura mater. A new experimental period started after which the animals were sacrificed.

The histological evaluation of the obtained material revealed the following course of tissue reactions: After 3 weeks the formation of an interfacial layer between bone of the skull and the augmentation was observed. It consisted of well vascularized connective tissue, for the greater part without osteoclasts or other signs of resorption. This interphase layer was gradually replaced by newly formed calcified tissue. The replacement was observed to be partially effected after 13 weeks and to be almost totally completed after 22 weeks. However, remnants of the original interphase persisted up to 29 weeks in some locations.

A beginning of ingrowth of soft tissue into the pores was observed after 3 weeks. This was accompanied by an acute inflammatory reaction due to some cell necrosis in the deeper part of the augmentations. After 13 weeks no necrosis was observed anymore, all pores being filled with healthy soft tissue; the invasion of the cement by hard tissue had started. The rate of hard tissue penetration appeared to depend on the absence or presence of the tabula externa of the skull bone: when the cortical layer was removed prior to applying the cement,a statistically significant higher rate of bone ingrowth was observed as compared with the situation when the cement was applied directly to the untreated skull bone.Table 5.7 compiles these observations after various experimental periods. In Fig. 5.12,the histological picture as found after 52 weeks is shown.

The presence or absence of periosteum did not exert any influence on the rate of bone ingrowth. In those cases where the periosteum was replaced over the augmentation,it was broken down within 3 weeks. The soft tissues of the scalp became attached to the augmentation by ingrowth of connective tissue.

The defect fillings, although clinically stable,did not appear to be invaded by bone even after 32 weeks. Bone necrosis at the defect margins was observed and the necessary remodeling process was still going on after this period. It is assumed that thermal damage, due to removal of the biopts by rotating instruments, had seriously retarded the (re)generation of new bone at the defect margins in those experiments.

Table 5.7.

Average maximal depth of hard tissue ingrowth measured in μm. Sample size in parentheses.

exp. period weeks	tabula externa present	absent
3	0 (4)	0 (4)
13	200 (2)	2150 (2)
22	1225 (6)	1900 (5)
29	900 (2)	1900 (2)
52	1600 (2)	3350 (2)

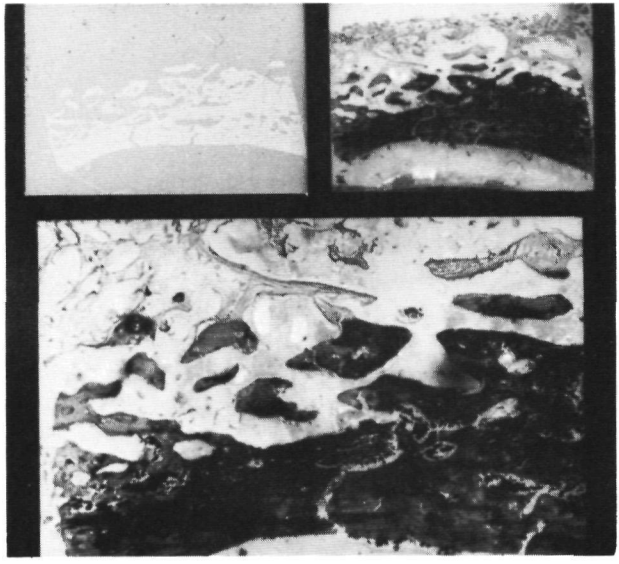


Fig. 5.12 Bone ingrowth (dark) in pores of augmentation (c). Top right: overview. Top left:microradiograph of same area. Below: magnification 3x

The conclusions are that the porous cement promises to be suitable as a material for the augmentation of cranial bone; especially when the cortical top layer is removed, the cement becomes rapidly attached to the underlying bone.

The only reservation to be made concerns immune response reactions; in a few instances, foci of chronic inflammation were observed which raised some suspicion of being caused by immuno-defense mechanisms.

It was decided to study part of this aspect in more detail (See section 5.4). The defect-experiment failed to give the desired information probably because of reasons not relevant to the cement. However, the absence of clinical signs that the relatively large defect fillings were not functioning or were not tolerated by the vulnerable underlying tissues, justify repetition of the experiment.

Both these clinically oriented studies of Ypma and Vaandrager seem to confirm the results described in section 5.1 as far as histological reactions are concerned. Overlooking the various outcomes, it seems to be justified to make the conclusion that in situ curing porous acrylic resin as obtained with 7% CMC of the ZHF-50 type in the aqueous phase, is not less and may be even more biocompatible on the level of cells of hard and soft animal tissue than the traditional solid bone cement.

On a more systemic level, harmfull influences may possibly be exerted by monomer contamination during and in the first time after the curing of the material in situ. The next sections of this chapter deal with the concentrations of monomer in the bloodstream after a simulated hip arthroplasty and with cell mediated immune reactions of the skin after implantation of the cement.

5.3 Monomer concentration in the blood stream after simulated hiparthroplasty in dogs

As has been discussed in chapter 4, the major concern that accompanies the use of acrylic resins as implant material is the possible contamination of the biological system with monomeric methylmethacrylate.

In section 4.3. and 4.3.1, it has been shown that, although the residual monomer content of porous cements is of the same order or even less than that of solid cement, the rate at which the monomer diffuses out of porous cement is initially higher than in the case of solid cement. This early monomer release may be of importance in those implantations where the compound can easily be introduced in the circulatory system.

In hip arthroplasty, for instance, a large part of the femoral vascular system is damaged by reaming the medullary cavity. When the acrylic dough is subsequently introduced to cement the prosthesis in place, monomer can be - and is shown to be - picked up by the damaged venae and is led "downstreams" into the vascular system. Numerous authors (e.g. Homsy 1971, McLaughlin et al. 1973, Pahuja et al. 1974, Modig et al. 1975) have measured the monomer concentrations in the blood stream after this operation either in man or in animal experimentation. The obtained data could be compared with the levels at which other authors (see section 4.2) had measured cardiovascular and respiratory effects after infusions

of known doses of the compound. The values which are most frequently found in this kind of experiments range from traces to 3 mg monomer per 100 ml of blood (3 mg %), depending somewhat unpredictably on sampling site (vena cava, vena femoralis) and whether measured in venous or arterial blood.
As the hip arthroplasty is undoubtedly the implantation where the system is exposed maximally to monomer contamination and because of the availability of so much data, it was decided to perform a similar experiment to compare porous cement with traditional solid cement as to monomer release.

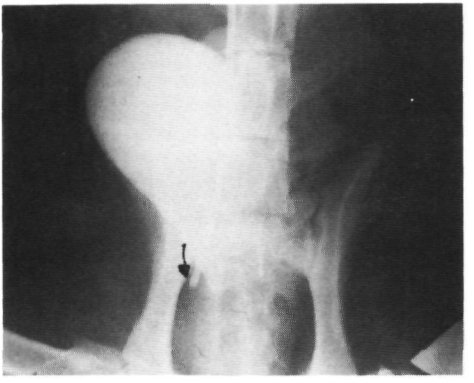
To this purpose, Labrador dogs were operated, using the usual but standardized surgical techniques, to expose the proximal part of the femur. A hole was drilled in the cortex, extending into the medullary cavity and large enough to introduce a 7 mm (outside diameter) teflon tube for reaming and subsequent filling of the medulla with cement. About 10 cm length of the medullary cavity was reamed by suction and filled retrogradely with solid (Sulfix-6) or 50% porous cement using a cement syringe. Prior to operation, a catheter tube had been introduced into the common iliac vein of the leg to be operated, approaching it from the jugular vein and vena cava. Care was taken, using X-ray contrast fluid and continuous radioscopy, to place the tip of the catheter tube a few centimeters upstreams of the place where the vena cava bifurcates into the common iliac veins. Blood samples of 10 ml each were drawn through the catheter tube at 1, 2, 4, 6 etc. to 20 min. after the cement had been introduced in the femoral cavity. The blood samples were placed in ice cooled, screw cap closed, glass test tubes containing 2,5 ml of 3,8 % trisodium citrate solution as an anticoagulant.
After all the necessary blood samples were taken, the catheter was removed and the wound sutured. The dogs survived the operation well and were kept in observation for at least three months. X-rays of the operated legs - each dog received solid as well as porous cement - were taken at regular time intervals. Immediately after the operation, the obtained blood samples were extracted with n-hexane using 1 ml on 5 ml of blood. The layers were allowed to separate and the hexane solution was analyzed on a Packerd Becker 419 gaschromatograph. A stainless steel column, 1/8'' x 3 m, filled with Chromosorb WAW/DMCS, 80-100 mesh, coated with 25% Emulphor 870 was used. The column temperature was 140°C and N_2 was used as a carrier gas at a flow of 7 ml/min. The attenuation was 10 x 4 and the retention time 9 min. The flame ionization detector burned on a H_2-compressed air mixture. The procedure was calibrated using aqueous solutions of the monomer and ethylmethacrylate was added as an internal standard. Table 5.8 compiles the data obtained in this way.
From these results two conclusions can be made:

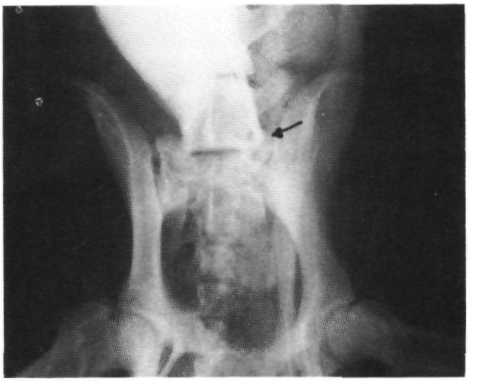
1) Generally the level of the values found is not different from those reported in the literature and no significant difference between porous and solid cement can be detected.
2) The detected levels are extremely dependent on the position of the catheter tip. The source of error introduced by inaccurate positioning of the catheter easily overshadows differences due to varying materials or operation techniques.

Table 5.8
Monomer content in blood of dogs after hip-arthroplasty

No.	cement	monomer content (mg(%)) at period after implantation								remarks
		1	2	4	6	8	10	12	20(min)	
1	porous	0	0	0	0	0	0	0	0	1)
2	porous	<0.2	<0.2	<0.2	0	0	0	0	0	
3	porous	4.5	2.5	0.4	0.2	0.2	<0.2	<0.2	0.2	2)
4	solid	-	0.4	0.3	<0.2	<0.2	<0.2	<0.2	0	
5	solid	0.7	0.2	0.2	0	0	0	0	0	
6	solid	<0.2	0	0	0	0	0	0	0	1)

1) catheter tip in vena cava
2) catheter tip, too deep in iliac vein, caused obstruction





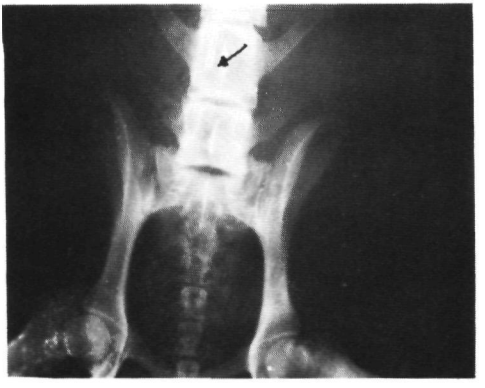
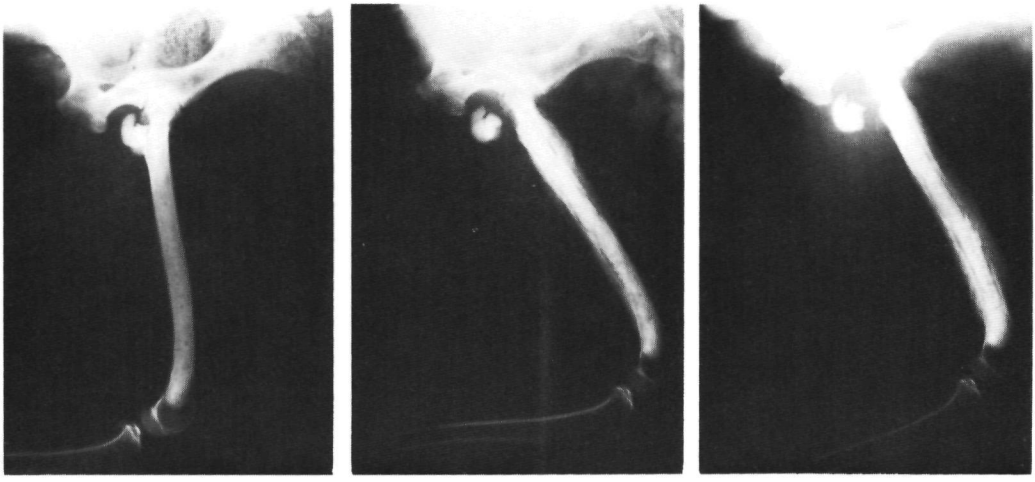
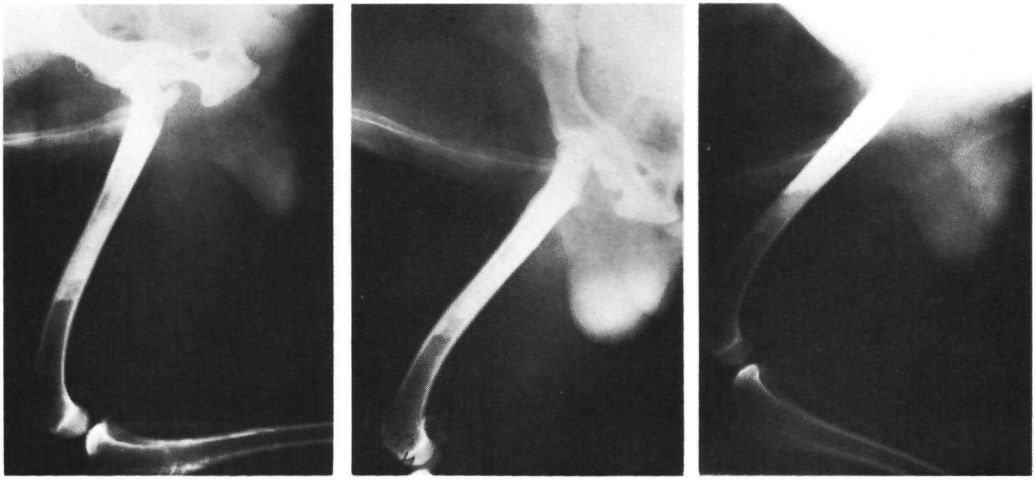


Fig. 5.13 Different positions of catheter tip (arrows).
A. catheter too deep in vena iliaca
B. catheter correctly placed
C. catheter in vena cava



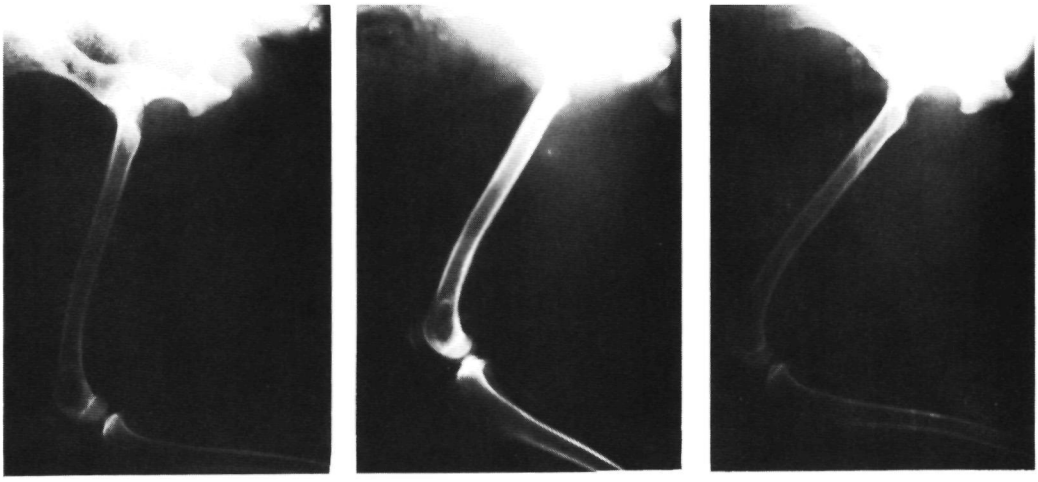
S(0) S(47) S(80)



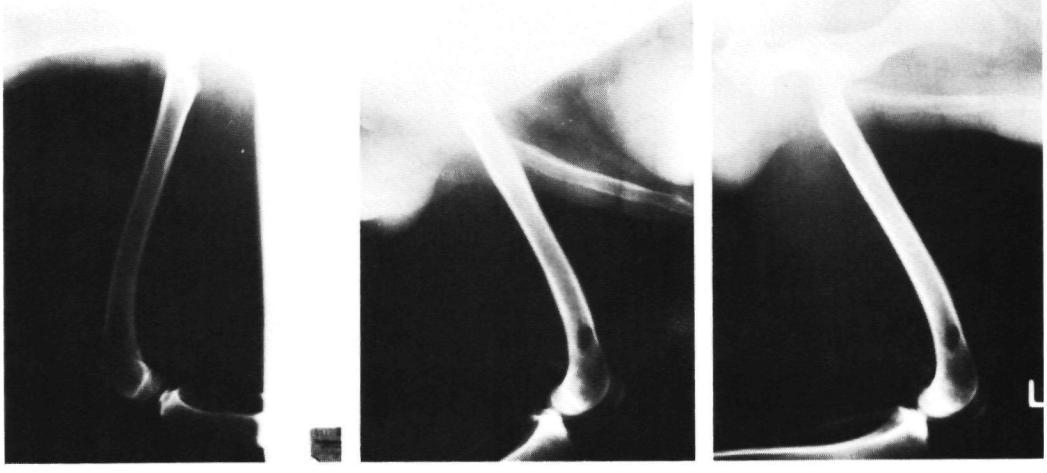
S(0) S(51) S(100)

Fig. 5.14A

2 canine femurs filled with solid cement (s).
The values in parentheses give the time(days) postoperatively.
Note radiolucent lines around the (radiopaque) cement.



P(21) P(53) P(110)



P(0) P(62) P(105)

Fig. 5.14B

2 canine femurs filled with porous cement (50-7) The values in parentheses give the time (days) post operationem. The porous cement is radiolucent. The apparent radiopacity in P(62) and P(105) is a photographical artefact.

The radiographs of Fig. 5.13 show how positioning differences of a few centimeters can occur, even if extreme care is taken during insertion. Fig. 5.13A was the situation responsible for the obstruction of the iliac vein in case No. 3. Fig. 5.13C shows the catheter tip in the inferior vena cava where the monomer is diluted to levels not detectable by our technique (case No. 1 and No. 6). Both displacements of the catheter from the ideal situation of Fig. 5.13B occurred during manipulating of the animal after the insertion procedure.

As has been discussed before, the systemic action of the monomer is directed to the heart and the lungs. The results of these experiments indicate that when the monomer arrives in the neighbourhood of these organs it will be diluted to levels of concentrations far less than necessary for untoward effects. Indeed, neither using porous cement nor in the case of solid cement changes in heart rate, and blood pressure could be detected in the time immediately following insertion of the cement.

The radioscopic follow up revealed the following facts: One femur, filled with solid cement, showed a massive ectopic calcification beginning at about 4 weeks and lasting up to 15 weeks (Fig. 5.14A). Although cement leakage had occurred in the joint region, which much has hindered the animal in using the leg, the phenomenon of subperiostal bone apposition is a frequent finding after intramedullary procedures.

Feith (1976) gives a thorough discussion on its possible causes which most probably lie in the disturbance of the medullary vascular system and the subsequent reaction of the periostal vascularization.

The other femurs in Fig. 5.14A and B show a more moderate and transient behaviour in this respect. The femurs filled up with porous cement (Fig. 5.14B) seem to have suffered the least disturbance of their cortical structure by the implantation. It is another indication of the porous gel cement being not less and even more biocompatible than solid acrylic cement.

5.4. Immune reactions to solid or porous PMMA implants in guinea pigs*

It has been discussed in section 4.1.2 that monomeric methylmethacrylate is capable of causing an immune response. The initial expectation that porous acrylic cement would release, due to its larger specific surface, residual monomer in larger quantities and at higher rates than solid cement, combined with some observations on cellular level in cranial augmentations (see section 5.2.2), led us to the choice of studying the allergic potentials of porous and solid cement. The study should also encompass benzoylperoxide, hydroquinone and dimethyl-p-toluïdine because the higher specific surface of the porous cement can be expected to cause higher release rates of the auxiliary compounds, which are also known as allergens, as well.

For this study - the details and results of which are given by van Mullem et al. (1981B) - the albino female guinea pig

* This study was done under supervision of Dr.P.J. van Mullem, Dpt. of oral Histology of the University of Nijmegen.

was chosen as an animal model on which skin patch tests were performed. The essentials of the experimental protocol consisted of pre-sensitization (induction) of the animals with methylmethacrylate, followed by implantation of the cement in the dermis of the back of the animals (2,5 gr/kg) whereafter two series of patch tests were made: one series 14 days after implantation and the other series 28 days after implantation. The reaction of the skin in terms of the severity of erythema or eventual edematous swelling was scored according to a ranking scale. The design of the experiment included the possibility to differentiate between toxic action and sensitizing potential of the compounds.
Seventy eight animals were used, which were divided in five groups:

1. Controls: No induction (pre-sensitization), no implantation
2. I/- : Induction, no implantation
3. I/S : Induction, implantation of solid cement
4. I/P : Induction, implantation of porous cement
5. -/P : No induction, implantation of porous cement

The scores of the various groups after a first patch challenge with MMA were statistically tested for significant differences, which led to the following results: the pre-sensitized and implanted animals (I/S and I/P) did not react more severely than the animals which only received pre-sensitization (I/-), perhaps with the exception of the I/P group, which showed a small tendency ($p=0.066$) to develop a stronger reaction in one particular area of the test field. The groups of animal which were pre-sensitized (I/-, I/S and I/P) exhibited significantly stronger reactions than the controls ($p=0.01$-0.001. That this difference with the control group is caused by the pre-sensitization and not by the implants, is confirmed by the fact that the I/P group reacted stronger ($p=0.03$) than the animals which only received a porous implant and no induction (-/P).
After the second patch test with MMA the I/- group showed generally stronger reactions than the reactions after the first test. This indicates a sensitizing action of the first patch test in this group. Also the I/P group showed this effect but only in one particular area of the test field. The other groups of animals did not display this so called "booster-effect". In Table 5.9, these results are summarized in a semi-quantitative way by assigning ranks to the mean scores (severity of reaction) of the groups.

Table 5.9. Ranking of skin reactions to MMA

Group	1st patch test	2nd patch test
Control	1	1
I/-	2	4
I/S	3	3
I/P	3	4
-/P	1	1

1→4: Increasing severity of reaction (mean score ranked on the basis) of the found significant differences.

The reactions on patch tests with the auxiliary compounds (benzoyl peroxide, hydroquinone and toluidine) were, without exception, of toxic origin. No indications were found that the animals were sensitized for these compounds by implantation of the cements.

With regard to MMA, the conclusions that have been drawn from these results (van Mullem et al. 1981B) state that the implantation of solid or porous cement did not sensitize not pre-sensitized guinea pigs. In presensitized animals the implants were not found to enhance sensitization, although there is some reason for suspicion that the porous cement has a somewhat greater potential in this respect than solid cement.

5.5. Conclusion of the biological evaluation

In the preceeding sections the expectation that the porous gel cement, due to larger specific surface and possibly higher monomer content, would turn out to be less biocompatible when implanted than solid cement is expressed several times. However, none of the described animal experiments has provided results that could confirm this hypothesis. Provided the pores in the cement are large enough and the used CMC powder is purified by extraction, neither the aqueous gel nor the monomer which is dissolved in it, nor the higher initial release of monomer appear to provoke less favourable reactions on cellular or systemic level when compared with the traditional solid bone cement. On the contrary, especially the histologic reactions of bone to the porous cement seem to be of a more favourable nature than when solid cement is implanted; this is indicated by the experiments in the forehead of swine and the results of the intramedullary fillings in sheep and dogs. In its general context the histological results confirm the preliminary observation of Feith (1976) who attributed the more favourable reactions of bone to the lower polymerization temperature occurring in the porous cement. The experiments described in this chapter were not designed to detect reasons for worse or better behaviour of the cements. However, the establishment of the fact that the initially higher release rates of monomer do not interfere with a rapid acceptance of the porous implants by the biological environment cannot contradict the above mentioned conclusions of Feith. Also the hypothesis of Huiskes (1979), stating that the combination of monomer and high temperature is to be feared in the use of bone cements rather than the action of one of the noxious influences separately, can be sustained by our observations.

The only area where particular attention is necessary until more information is obtained, is the allergic potential of the porous cement which might be slightly higher than that of solid cement. The indications underlying this suspicion, however, are vague and in practice distinct cases of sensitivity to solid acrylic resin implants occur at a very low frequency. Combined with the mentioned favourable histological results the conclusion is warranted that in situ curing porous acrylic cement - prepared by means of a 7% solution of purified CMC (of the type NYMA ZHF 50) in relative quantities of not less than 35% W/W and not more than 50% W/W

and provided the monomer and polymer have the composition as described in chapter 2 - can be applied safely in human clinical situations where augmentation, substitution or suppletion of bone is desired and high mechanical stresses need not to be expected. In this composition, the cement will also allow for ingrowth of healthy mineralized tissue, thus offering possibilities for enhanced implant fixation.

The next chapter will describe biomechanical experiments, the results of which will help beacon the areas of possible application more precisely.

CHAPTER 6. BIOMECHANICAL EXPERIMENTS

6.1. Introduction

The mechanical properties of the porous bone cement have been given and discussed in section 4.4. The obvious lower strength values found for the porous cement carried us, already in an early stage of the development, to the conclusion that these materials as such would not enable direct replacement of solid cement in all its traditional applications. On the other hand it was shown that the accompanying decrease of stiffness may compensate partly for the lower strength in loaded constructions by giving rise to lower stresses in the porous material. Additionally, it was stipulated that after ingrowth of bone the stress pattern in the resulting bone-cement "composite" would be drastically altered upon loading and renewed biomechanical analysis would be necessary to predict the performance of the cements in such a situation.

The elaborate theoretical analyses of Huiskes (1980) made for the well known cemented hipprosthesis have been referred to earlier in this work. It provides an example of how the mechanical performance of a construction and parts of it can be estimated when material properties and geometrical parameters are given. It also provides, however, the instruments to improve such a construction when weak spots are predicted or to adapt the geometry of the construction to an eventual unavoidable shortcoming mechanical parameter. Staying with the case of the femoral endoprosthesis, Huiskes' calculations showed that the highest stresses will occur at the metal prosthesis - cement interface in the proximal and distal regions of the implant. Much lower stresses can be expected at the bone-cement interface, being minimal in the middle part of the structure.
At the bone cement interface,on the other hand, there is the problem that the biological and man made materials do not adhere, do not adapt very closely - becoming separated by a soft tissue membrane - and seldom show more mutual fixation than a superficial entanglement. Loosening as a consequence of an unstable implant and resulting bone resorption is, in addition to mechanical failure of implant components, the reason for many late complications of this otherwise so salvaging arthroplasty.
One of the conclusions of Huiskes was that the cemented hip prosthesis construction could probably be improved by providing more strength, using prefabricated acrylic polymer collars and thicker cement layers, to the proximal and distal regions of the cement mantle and by applying porous cement at the bone-cement interfaces, especially in the middle part of the construction, to accomplish better bone-cement fixation. A very appealing aspect of his suggestions is that in this way differing problems - constructional strength and inter-

facial biomechanics - are coped with by differing and thus more adequate means.

The theoretical outcomes seem to be confirmed by experiments of Ypma et al. (1979) and Ypma (1981). As will be reviewed in chapter 7, this study consisted of

1) cementing total hip prostheses in sheep using solid and porous cements and
2) in vitro biomechanical testing of solid and porous cements in a simulated hip arthroplastic construction.

The animal experiment learned, after post mortem examination and histological evaluation, that the porous cements had a remarkably more intimate adaptation to bone, that had also grown into the pores, than solid cement, which was separated from it by a connective tissue membrane. At the cement-prosthesis interface, however, the porous cement had failed mechanically contrarily to the solid cement. The biomechanical test revealed that 35% porous cement could effectively be stress-shielded by separating it from the prosthesis stem with a layer of solid cement.

The considerations given above lead to the conclusion that the mechanical properties of the porous cements per se do not give enough information to judge about possible applications. Herefore, an evaluation should encompass structures surrounding the materials. It would be out of the scope of this work to give elaborate biomechanical analyses of implant constructions. In the following sections, some elementary data will be given concerning the influence of ingrown bone on the porous cement properties, on the obtained interfacial strength and on the recovery of strength of bone that had received a porous cement implantation.

The experiments were performed in the os parietale of swine (sus scrofa) where the quantities of cancellous bone (See Fig. 5) allow for preparing relatively large cavities and defects without traumatizing the animal too much. Moreover, this implant site is practically free of mechanical stresses, so that this variable cannot confuse the information obtained.
The procedure of the operations is, in essence, similar to what is described in Chapter 5 (histologic evaluation).

6.2. Flexural strength of porous cement before and after bone ingrowth

Some insight in the interesting question whether locally in a porous material the stress resistance will be increased by ingrown bone, can be obtained by comparing the strength of a piece of porous material before and after bone has grown in it.
For this purpose, flexural strength was chosen as the most significant property, not in the last place because of the small specimens that can be tested when proceeding according to DIN 53452 as described in section 4.4.2.3. Cavities measuring 5 mm in width, 15 mm in length and 12 mm in depth were prepared in the osses parietale of a swine using a trephane at low speed , chiseling the cavity-walls

to the proper dimensions (Compare fig. 6.2.B). Four cavities were filled with 50% porous cement (mean pore size 600-700 μm). The material was left in place for 26 weeks. After sacrifice of the animal the implants were harvested and milled and finished to rectangular specimens of 15x10x2 or 3 mm. For comparison similar specimens were prepared from spongious bone as was present in the direct vicinity of the implants.
Microscopical examination of the obtained cement-bone pieces revealed that bone ingrowth had been approaching near completeness, as unfilled pores could only scarcely be found. Because of the small quantity of material available (4 specimens) no attempt was made to quantify the volume of ingrown bone exactly. Fig. 6.1 shows a fragment of a test specimen after failure.

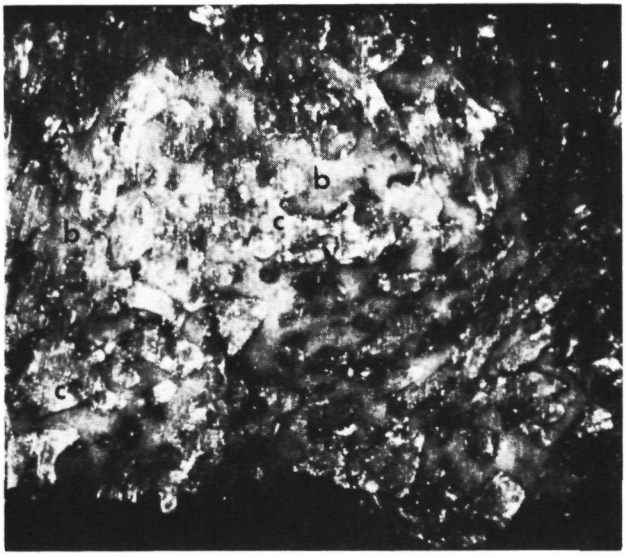


Fig. 6.1. specimen after failure in flexural test showing closely interwoven cement (c) and bone (b).

The results of the test are given in Table 6.1, including the flexural strength of 50% porous cement that had not been implanted. The measured strengths as well as the bending angles at which fracture occurred seem to indicate that the properties of the bone-cement composite tend to values close to the average of the bone and the cement properties.
It should be born in mind however, that the bone cement composite consists of two interwoven matrices from which the bone matrix is considerable more rigid than the cement matrix. Assuming that there is only a low degree of mechanical interaction between the two

matrices, the best interpretation of the data of Table 6 is probably that the measured strength of the composite is actually the strength of the bone matrix.
For practical purposes, however, the conclusion must be that in the volume taken up by a porous cement implant the resistance against stress will increase with time passing (i.e. by the formation of a bony matrix).

Table 6.1 Results of flexural test

	Flexural strength MN/m^2	Angle at fracture
unimplanted cement (50-7)	7.2 (1.0)	11°
cement after bone ingrowth	13.0 (5.0)	9°
surrounding bone	19.6 (3.0)	7°

Values in parentheses are 95% confidence intervals of the mean.

6.3 Interfacial strength

When the function of porosity in an implant is the enhancement of the fixation between implant and the host tissues, quantification of the quality of the obtained fixation is of interest. To obtain this information,the strength of the interface between tissue and implant should be determined in shear or in tension.

A common way to test the strength of the fixation between bone and implant is to perform a so called "push-out" test ,in which the force necessary to push a cylindrical implant axially out of the embedding bone is determined. Dividing this force by the interfacial area gives the push-out strength which, theoretically, should equal the shear strength of the interface.

Another way, less common, is to apply the force perpendicular to the interface giving information about the tensile strength of the fixation.

In animal experimentation,both types of test were performed for the case of 50% porous cement in bone. Again the os parietale of swine was chosen as the implant site. For the push out test cylindrical cavities (5mm in diameter, 10mm depth) were prepared with a trephane bur. Four cavities for each experimental period were prepared as shown in Fig. 6.2A. Prepolymerized cylindrical implants 5mm diameter and 10mm long were made of 50-7 cement (PP-L-7 according to the notation in Table 5.1 and implanted "press-fit"" in the cavities. After the experimental period (ranging from 3 to 15 weeks), the implant was recovered burried in a block of surrounding bone. This block was finished in such a way that two parallel planes were obtained at the upper and lower side of the implant. The surfaces were ground away untill the full diameter of the implant was visible.

The force necessary to push the implant out of the surrounding bone was then measured on an Instron testing machine using a cross-head speed of 0.5 mm/min. Care was taken that the direction of the applied force was opposite to the direction of the implantation, thus ensuring that any undercuts initially present were unlikely to influence the results.

For the tensile test rectangular cavities were prepared by using a trephane bur and chiseling the cavities to the dimensions of 15x10x5 mm (Fig. 6.2B). After filling with in situ curing 50-7 cement, the implants were left in place for 26 weeks. The bone plate containing the cement was retrieved and sawed and finished to specimens consisting of two layers of bone separated by a layer of cement. An example of a specimen obtained in this way is shown in Fig. 6.2C. The specimens were fixed in the clamps of an Instron testing machine and loaded in tension, perpendicular to the bone cement interfaces, at a crosshead speed of 0.5 mm/min. The results of the push out test and the tensile test are given in Table 6.2.

Table 6.2
Push out strength and interfacial tensile strength between porous cement and bone.

Exp. period (weeks)	Push-out strength N/mm^2	Tensile strength N/mm^2	Bone[1] ingrowth
3	0.1		-
6	1.42		$\frac{+}{-}$
	0.67		$\frac{+}{-}$
10	0.75		++
	0.67		++
15	1.44		+++
	0.75		+++
26		0.64 (0.11)[2]	+++

1) according to table 5.7
2) mean value and standard deviation of 4 specimens

The absolute values found for the push out strength are, again, difficult to interpret because of the many mechanical and geometrical parameters involved. The relatively low level of strength will at least partly be caused by the low strength of the porous cement. Clemov et al.(1981) reported values in the range of 3-8 N/mm^2 found in a similar test with porous titanium implants. This is an order of magnitude higher than the results with porous cements which correlates with the difference in strength between both materials. It is remarkable, however, that in our experiment the push out strength does not seem to increase significantly after 6 weeks. Apparently, the superficial ingrowth at this stage was at least complete along the circumference of the implant. The longer experimental periods resulted in additional bone ingrowth deeper inwards

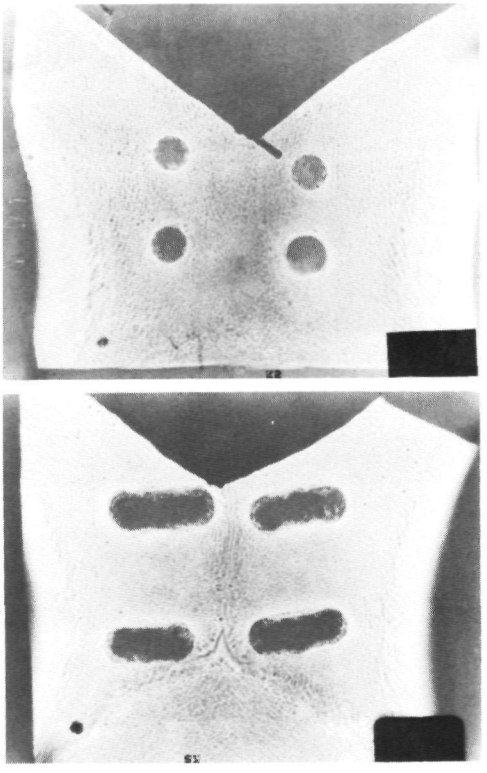


Fig. 6.2A. Cylindrical cavities in the os parietale of swine after resection. The formation of a lamina dura around the implant and ingrowth of bone is distinct (26 weeks)
B. Idem. These cavities were made for flexural and tensile tests as described in sections 6.2 and 6.3.
C. example of a tensile specimen after failure.

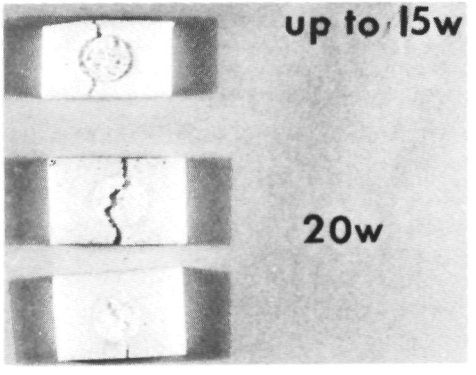


Fig. 6.3 Specimens of bone containing porous cement implant after failure in a flexural test. Only in the 20 w. specimen the fracture surface protrudes through the implant.

in the implant, which did not contribute to a higher interfacial strength.

The tensile test does not seem to give much additional information, the strength as measured in tension being of the same order of magnitude as the push-out strength. The low value for the interfacial tensile strength, as compared to the flexural strength of the bone-cement composite (13.0 N/mm^2, Table 6.1) and the tensile strength of the porous cement itself (2.2 N/mm^2, Table 4.1), is unexpected and provides another example of the complex way in which material properties determine the performance of constructions.

6.4 Recovery of strength in defected cancellous bone.

An obvious way to cope with the difficulties in predicting the performance of implant bone constructions is to design experiments in which integrated assemblies of the materials involved are subjected to mechanical loads. As one of the major potential applications of the porous cement is the substitution of bone in the case of defects, it is of considerable interest to obtain some knowledge about the recovery of strength of a certain volume of bone in which a defect has been filled up with porous cement.

To this purpose cylindrical defects, 5 mm in diameter, were made in the already described implantation site. The defects were filled with in situ curing 50-7 cement and left in place for periods ranging from 3 to 20 weeks. Retrieval of the implants, together with surrounding bone, was followed by preparing flexural bone specimens (15x10x3 mm) containing the defect in the geometrical centre. The defect took up about 13% of the specimen volume. Fig. 6.3. shows some of these specimens after failure in the flexural test. For comparison, intact specimens, obtained from bone in the direct vicinity of the implants were prepared for each experimental period. Table 6.3. summarizes the results of both series of measurements.

Table 6.3 Flexural strength of defected and intact bone

Exp. period (weeks)	Flexural strength (N/mm^2)	
	bone with implant	intact bone
3	4.9 (1.3)	12.8 (6.9)
6	11.1 (0.1)	15.3 (6.1)
9	14.5 (0.6)	14.5 (2.1)
15	16.0 (0.7)	17.1 (5.1)
20	18.4 (1.7)	18.1 (5.3)

Mean values calculated from 3 to 6 samples;
standard deviations in parentheses.

The data suggest a very early recovery of the flexural strength; the values for defected bone and intact bone do not differ significantly ($p > 0.20$) already after a period of 6 weeks. This is in marked contrast to what is known from clinical experience in cortical bone which is defected by screw-holes in cases of internal fixation of fractures with plates etc. Claes et al. (1981) for instance, found a recovery of the tensile strength of only about 20% after 12 weeks in the case of holes drilled in cortical bone (tibia) of sheep. In this experiment the artificial defects were left unimplanted as is the common way to do in clinical cases.
In comparison,our experimental results would suggest a beneficial influence of filling up the defects with porous cement. Some reservations must be made, however, for the results of our experiment. The defects were made in spongious bone (the os parietale of swine) and examination of the test specimen revealed that the early recovery of strength is probably due to the formation of a layer of condensed bone in the peri-implant region. This layer is clearly visible in the radiograph of Fig. 6.2A. Its formation preceeds the ingrowth of bone during a period of 3-6 weeks of implantation, which was one of the observations of van Mullem et al. (1978) described in section 5.1 (Table 5.4). Undoubtedly, this "lamina dura" will have strengthened the spongious specimen considerably in this early stage. Moreover, the fracture surfaces invariably did not protrude through the implant until 20 weeks after implantation. Only then bone-implant integration had proceeded so far that fracture occurred through the implants, rather than around it. Fig. 6.3 illustrates these phenomena by showing examples of the fractured test specimens. It can be doubted whether the formation of this layer of condensed bone would strengthen cortical bone as well in these early stages because of the similarities between both types of bone. Nevertheless, this test reveals that the porous cement is effectful in bridging an osseous defect in cancellous bone in the sense that the bony structure can recover its original strength in a relatively short time.

CHAPTER 7. POTENTIAL APPLICATIONS OF THE POROUS CEMENT

7.1. General considerations

In the foregoing chapters it has been mentioned that, due to the impaired mechanical properties, the porous gel-cements cannot be regarded as a substitute for solid acrylic cement in all its traditional applications. The large difference in mechanical characteristics excludes direct interchangability.
The merits of the porous cement can rather be found in improved "interface-compatibility" in comparison with solid cement, due to the lower temperature maximum when curing and to its capacity to form an interwoven network with ingrown tissue. The latter aspect offers the opportunity to obtain implant-tissue fixation with improved prognosis while the lower peak temperature will help the adjacent tissues to overcome the trauma of implantation in shorter time. The advantage of the cement over other porous implant materials may often be found in the processability in situ.

For these reasons, potential clinical applications of the cement should be sought in substitution or suppletion of tissue in those areas where low mechanical stresses can be expected. The cement may also serve as a means for anchoring prostheses to bone, when provisions are made to shield the material against large mechanical stresses. In the following sections, some concrete cases of possible applications will be discussed.

7.2. Filling of defects in bone

Defects in bone can be caused by trauma, by treatment for pathology involving removal of impaired tissue, after bone transplantation or after surgical procedures necessary to obtain access to organs etc. In many of these examples, a defect will be left which is too large for the biological system to overbridge effectively by regeneration of bone. Either the defect will not become closed at all or, in filling up with new bone, the original geometry of the bony structure is lost definitively, thus affecting mechanical or other functional characteristics. In such cases, application of the porous cement will serve two purposes: immediate closure of the defect and offering a geometrical matrix for the regeneration of new bone. Moreover, it has been shown (See section 6.4) that a piece of bone containing a relatively small defect, which is filled with 50% porous cement, can regain much of its original strength in short time.

7.2.1. Cranial defects

Defects in the human skull can occur as a cause of the events mentioned earlier. A prompt closure of such defects is almost always

indicated for reasons of protection of the underlying organisms against traumatization or infection.
The use of acrylic resin appliances to close cranial defects has been reviewed shortly in section 1.2. Porous cement might be preferable in many cases because of the expected better anchoring of the implant to the bony edges of the defect. Mention has been made of the work of Vaandrager et al. (1980) who explored the use of 50% porous cement for filling up artificial defects in the skulls of monkeys. (Section 5.2.2.) Although the principal item of the study(fixation of the implant to bone) was lost because of experimental artefacts, the potential of an effective closure was indicated by the animals surviving periods up to 1 year without clinical complications. Histological examination (Van Mullem, 1979) revealed the presence of loose connective tissue in the pores throughout the implant in a stable relation to underlying dura mater and overlying muscle tissue. When this aspect would be combined with bone growing in from the edges of the implant, the most conditions for an ideal defect filling would seem to be fulfilled.

In the case of very large defects, as can occur after treatment for malignities, for instance, considerations of mechanical strength might lead to a preference to use solid acrylic "inlays" instead of fully covering the defect with porous cement. Actually, this is one of the methods in cranioplasty which is frequently used to great satisfaction (e.g. Beumer et al. 1979). Exact contouring of the implants per operationem, however, is often difficult or asks for elaborate, time consuming procedures. The use of the porous cement in these cases to secure the implant to the defect margins might very well facilitate a smooth marginal adaptation. Moreover, ingrowth of bone into the porous cement can be expected to result in improved implant fixation.

7.2.2. Dental root implants

A common problem in the prosthetic treatment of edentulous patients is the continuing resorption of the alveolar ridge after tooth extraction. As this edentulous ridge gradually disappears,the remaining contours of the jaw offer less and less opportunity for stable retention of a full denture. Eventually, this resorption may proceed so far in elderly patients that fitting a denture becomes impossible without so called "preprosthetic" surgical treatment to restore the jaw's contour by bone grafts or allografts.
In order to prevent the alveolar ridge from collapsing after extraction,an old concept of intentionally leaving the roots of decayed teeth submerged in the body sockets is sometimes followed. The retention of endodontically treated or vital roots is generally believed to preserve the mass of the alveolar ridge. (Kabcenell 1971, Brewer et al. 1975, Garver et al. 1978).

When the roots are seriously decayed, periodontally affected or fractured, however, this concept cannot be followed. For this reason several investigators have studied the use of implants, serving as spacefillers in de alveoles after extraction, for prolonged conserva-

tion of the bony contours. Polymethylmethacrylate (Lam 1968, 1969, 1972), vitreous carbon (Mills et al. 1974, Missika 1977) and hydroxyapatite ceramics (Denissen 1979, Denissen et al.1980A) have been used to this purpose, invariably leading to the conclusion that contour preservation is indeed prolonged at least in this way.

Obviously, not only the presence of the implants in the bony sockets but also a stable histological relation between implant and surrounding bone is a criterium of importance in this application. Although mechanical strength is hardly a critical parameter in this context, a durable integration of implant and bone will be to the advantage of the stability of the implant. In this respect the hydroxyapatites seem to compare favourably with other solid implants because of the strong bond that is observed to be formed by the adapting bone (Denissen et al.1980B).

Certainly, porous implants with their ability to become invaded with bone are interesting materials for this purpose. The inadvertent finding of Peterson et al. (1979) that the porous acrylic root portions of fractured dental implants in dogs became readily burried in the jaw bone encouraged the exploration of the porous cement for this purpose. In a preliminary study Ramselaar et al.(1980) found that 50% porous cement applicated in fresh extraction alveoles in dogs was accepted favourably by the tissues. When wound bleeding and exudate could be prevented to lift the implant out of the pocket by proper fixation, the soft gingival tissues closed normally over the cement. After nine weeks bone was observed to overgrow the implant and ingrowth into the pores hard started as is illustrated by Fig. 7.1,

In addition to the easy processability of the cement as compared with solid implants (requiring trimming and finishing to fit the alveolar socket) these findings warrant further investigation of this application.

7.2.3. Other defects

Detailed discussion of all possible bone defects where the cement could enhance healing would be outside the scope of this chapter and lead to speculation. Mention should be made, however, of those defects which results in bone after removing tissue for autografts. In spite of the increasing availability of synthetic materials,there remain reconstructive treatments in which bone transplants are preferred over allografts for various reasons. In many instances the disadvantage of "filling a hole, leaving another" is counterweighed by the benefits of the treatment. Sometimes, however, the impairment of the donor site might cause discomfort for the patient in a physical or cosmetical sense.

One example is spinal fixation in orthopedic surgery. Some cases of disfunction of the spine require the fusion of two or more vertebrae to alleviate the patients complaints of pain etc. This fusion is frequently accomplished by interstitial pieces of bone which are taken away from the iliac crest. The use of another donor site would require an additional incision and is therefore not recommended. However, the contours of the iliac crest will often remain disturbed

after this treatment and the superficial position of the defect may cause discomfort to the patient in wearing his clothes or by being clearly visible. Recontouring of the crest with the porous cement is, obviously, a potential usefull application.

7.3. Augmentation of bone

Apart from the causes mentioned in the previous sections, shortage of bone in certain sites of the skeletal system can occur as a result of early developmental disturbances or gradual resorption, atrophia, etc. The suppletion of volume to these, otherwise intact areas with the purpose of restoring contours is called augmentation which, again,can be accomplished by the use of bone transplants or alien material. In the latter case,the risk of renewed resorption of the grafts is avoided and surgery can be constrained to the site to be treated. Fixation of the augment to the bone, however, offers the usual problems and poor securing of the implant may lead to its migration or mobility, thus compromising the proposed functioning. Additionally, the use of preshaped materials may render exact dimensioning a difficult task to perform.
Obviously, the porous cement has potential applications in this area. In the following section attempted application to cranial deformities will be discussed.

7.3.1. Cranial augmentations

Deformities of the cranial-maxillary regions have frequently to be corrected for cosmetical reasons. The usual methods of treatments and the problems encountered has been mentioned. In section 5.2.2. animal experimentation with cranial augments of the porous resin is described (Vaandrager et al. 1980). Fixation of the augment to the underlying bone was observed to occur by ingrowth of calcified tissue. Overlying muscle tissues became attached to the implant by connective tissue and no signs of dehiscense or exfoliation were observed during one year of experimentation. It is a remarkable fact that intact, stable bone can as yet be brought to growing into the pores of a material merely placed on top of it. Apparently, the surgical exposure and the noxe of the implant form a sufficient trauma to provoke remodelling of the tissues. This is sustained by the observation that the ingrowth rate was significantly higher when, prior to augmentation, the outer layer of cortical bone was removed, thus superficially further traumatizing the bone.
Encouraged by the favourable animal results, a clinical trial with selected patients requiring cranial recontouring was initiated by Vaandrager at the department of plastic surgery of the University of Rotterdam. The patients suffered from cranial deformities due to congenital assymetries, hemifacial athrophies, fibrous displasia, disposition after surgical treatment for other reasons,etc. Porous cement with 50 vol%. porosity was used in 12 of these cases invariably following the method of preparing superficial grooves in the bone before placing and curing the cement on it.

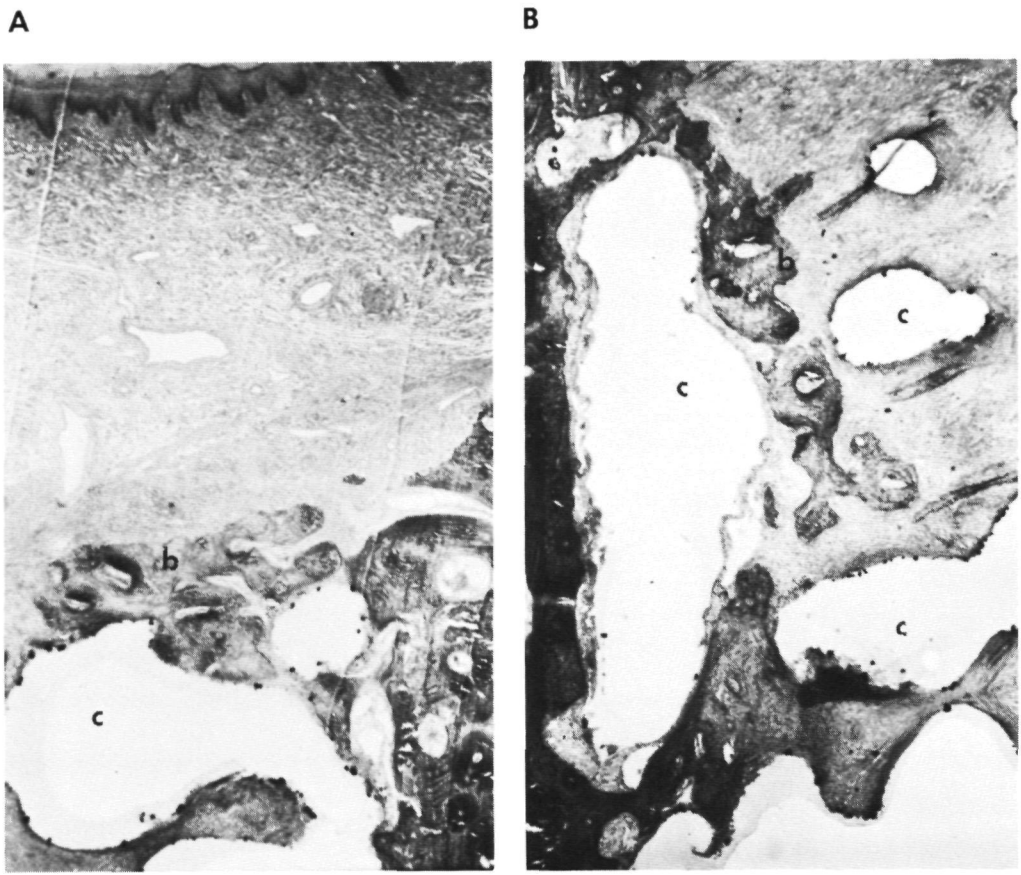


Fig. 7.1. A. Bone (b) growing over porous cement (c) in alveolar cavity in the jaw of a dog
B. Bone (b) growing into the pores of the cement (c).
The implant had been in situ for 9 weeks. (Ramselaar et al. 1980).

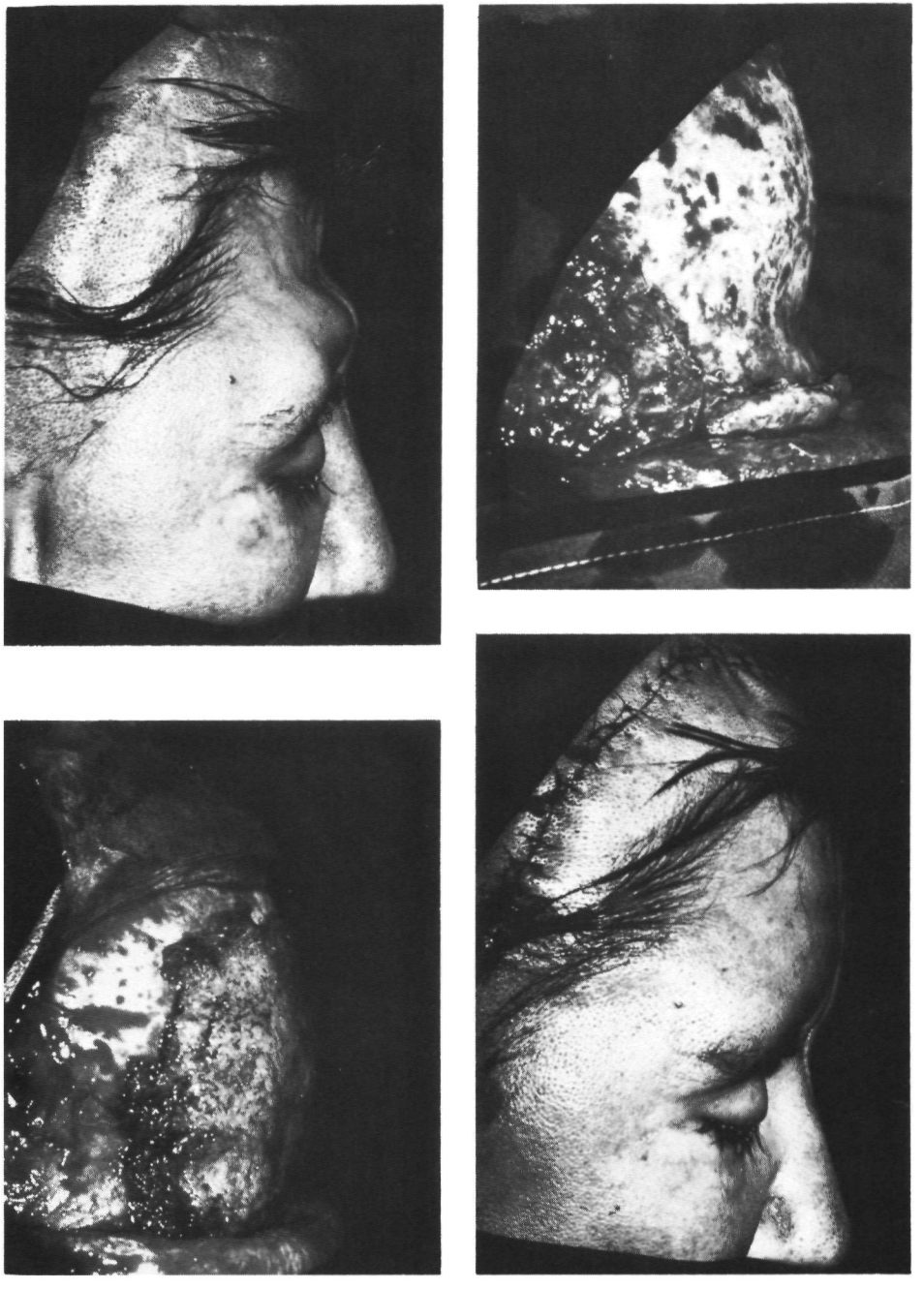


Fig. 7.2. Augmentation of frontal bone. Top: the retro-position before operation. Bottom: The result after applying the cement.
(Vaandrager et al. 1980).

In this way,provocation of the bone and providing means for immediate fixation was accomplished simultaneously. All the operations went uneventfull as to applying and countouring the cement, wound healing and recovery of the patients. The oldest augmentation is in place for three years at the moment of this wirting. Clinically stable implants and satisfactory cosmetical results are observed, with the exception of one patient who developed an infection one year after implantation and needed reoperation to remove the implant. The reason for the infection could not be detected: the retrieved material was found to contain Staphillococcus aureus, but this could also have been caused by contamination during the preceeding attempts to manage the infection by drainage etc. During removal of the implant,it was noticed that a part of the augmentation did not show any fixation to the bone. while an other part could hardly be distinguished from adjacent bone, the cement and the tissue being closely interwoven. It suggests that the infection must have been present for longer periods, inhibiting the bone to grow in locally, or destroying an earlier obtained fixation. Fig. 7.2 gives an example of a patient having a retroposition of frontal bone as a result of an earlier Le Fort III osteotomy which was succesfully corrected by the use of the porous cement.

7.4 Fixation of hip prostheses

In section 5.2.1 the biological response to the porous cement when implanted in the medullary cavity of the femur of a sheep was discussed. The conclusions of Ypma (1981) confirmed the enhanced interface-compatibility when porous cement was used to anchor a femoral prostheses, but expressed concern about the mechanical performance of the cement in this application.
The study was completed with an in vitro biomechanical evaluation of solid and porous cement performance in a hip simulation experiment. A man-made model of the human upper femur was developed using glass fiber-reinforced polyester resin to simulate human cortical bone and a "reversed" implantation procedure to ensure reproducible geometry and positioning of the femoral prostheses (de Wijn et al. 1979). Cyclic loading of the so obtained models in a specially designed testing machine revealed that in the traditonal construction, the mechanical response of the cements was what could be expected, considering their respective strengths. The compliance of the construction when submitted to cyclic loads of 3000 N was not observed to alter significantly over half a million cycles when solid cement was used but increased slightly to severely in the case cements with 35% resp. 50% porosity were used. The worst deterioration of the cement occurred at the proximal end of the prosthesis stem-cement interface as was observed in the earlier animal experiments.
However, when the prosthesis stem was provided with an inner layer of solid cement and an outer layer of 50% porous cement, the results of cyclic testing indicated a significantly increased stability of the compliance. It is expected that the use of a stress shielding layer of solid or prefabricated resin and a cement with somewhat lower porosity than 50% will be equal to solid cement in mechanical

performance. When this is added to the more favourable prognosis of the bone-porous cement interface, a fundamental improvement of hiparthroplastic treatment might very well be achieved.

A problem still to be resolved is the obtainment of a good adhesion between solid, stress-shielding resin and the porous cement. Curing of the porous cement against already cured, solid resin will generally not lead to fixation of the two layers because of a tendency of the aqueous gel in the porous cement to spread over the surface of the solid cement, thus inhibiting both materials to adhere.

A clinically usable procedure to overcome this problem might consist of an initial appliance of porous cement in the medullary cavity using a removable and enlarged "dummy" of the prosthesis stem to create a cavity in the porous cement. After hardening of the porous cement the prosthesis may be cemented in this cavity with solid cement, which can flow into the pores of the outer layer. An enhanced bond between both materials is provided by mechanical entanglement.

When the underlying concepts prove to be valid, the disadvantage of a two stage cementing procedure will be outweighed by the benefits of an improved interaction between bone and porous cement.

SUMMARY & CONCLUSIONS

This work describes essentially the synthesis, development and evaluation of a potential biomaterial: cold curing porous polymethylmethacrylate (PMMA).
In the field of biomaterials - i.e. materials used for substitution, enforcement or suppletion of lost and disabled parts of the human body - PMMA has had a long history. Chapter 1, section 1.2 describes this history including a survey of the areas in which the polymeric material has been and is still used clinically.

A current concept in biomaterials is the use of porous materials to enhance the fixation between the implanted material and the surrounding host tissues. It is well known that soft and hard tissue will grow into the pores of such a material - provided the pore size is large enough - thus anchoring the implant to the implant bed. In section 1.4 this concept is reviewed for a variety of materials and applications and the motivations are given for the development of a porous cement which would combine porosity with the possibility of in situ hardening of an initially plastic material. The only cement-like implant material that is used clinically is PMMA-cement (acrylic cement) which was introduced for surgical applications in the 1950's.

Chapter 2 reviews the principal routes to the synthesis of porous PMMA and the scarce attempts that have been made to obtain porous PMMA-cement. In section 2.2 our approach to the synthesis of a porous acrylic cement is described: the dispersion of an aqueous gel through the still uncured dough of a traditional bone cement. After hardening, a two phase material is formed, from which the aqueous phase can diffuse into the biological environment leaving a network of pores. Conceivably, these pores will raise the opportunity for the tissues to grow in. To this purpose, however, it is important to have control over the size of the pores, the interconnectedness of the pores and the size of the interconnecting pores. In chapter 3, the methods of determining these parameters are discussed and commented upon. Section 3.4 gives the results of measurements characterizing the porous structure of the cement and the influence of variables as gel-viscosity and relative gel-volume here upon.

Every potential biomaterial has to be investigated thoroughly on a variety of chemical and physical properties prior to any biological use as to gain insight in possible toxical or irritating influences which may be exerted on the biological host and to assess the capacities of the material to perform favourably in the applications aimed at.
The long clinical experience with solid acrylic cement has learned that unfavourable performance may be caused by two characteristic aspects of these materials: 1) the temporarily high temperatures which occur in the material due to the exothermic nature of the curing (polymerization) reaction and 2) the presence of low molecular weight

residues, particularly monomeric methylmethacrylate, in the hardened material. These general aspects of acrylic cements are discussed in chapter 4, section 4.1. Since the porous cement is a modification of the traditional solid cement, evaluation of the newly developed material with regard to these same items is of considerable interest. Section 4.2 and 4.3 give the results of this in vitro evaluation.

The mechanical properties of a biomaterial are critically determining the areas of application. Obviously, the mechanical properties of acrylic cement are compromized by the introduction of porosity and characterization of the new material in this respect is necessary. This has been done in section 4.4 by determining compressive tensile flexural and impact strength as well as the moduli and the influence of pore volume and pore size there upon.

Extensive animal experimentation is an indispendable part of biomaterials development. It should encompass histological investigations to the response of hard and soft tissues adjacent to the implant and measurement of the contamination of the biological system with ingredients of the implanted material in order to assess the degree of biocompatibility of the proposed material. Additionally, biomechanical and application - directed experiments are necessary to come to conclusions about clinical usefulness and eventual design parameters. Chapter 5 contains a report of such an evaluation made for the porous cement. Section 5.1 gives a detailed description of the histological response following implantation of the material in cancellous bone of swine. Unfavourable response such as inflammation, necrosis and resorption of animal host tissues, and the desired aspect of bone ingrowth has been determined as a funotion of pore size, material composition and time, resulting in the formulation of the optimal composition for a porous acrylic cement. Section 5.2 describes experiments in which possible applications in the field of orthopaedic and plastic surgery have been tested in sheep and monkeys.

Monomer contamination of the blood stream after implantation of cement in dogs has been measured and compared for solid and porous cement. The results are given in section 5.3.

Finally, an attempt has been made to compare solid and porous cements as to allergic potential, using guinea pigs, the results of which are given in section 5.4.

In chapter 6 biomechanical experiments are described resulting in the assessment of the strength of porous cement before and after ingrowth of bone (section 6.2) and in the quantification of the bone-implant-interface mechanics (Section 6.3). The recovery of strength in a volume of cancellous bone in which an artificial defect was filled with the porous cement has been determined; this has been described in section 6.4

The general conclusion that can be made, considering the results of the evaluations described in the chapters 3 to 6, is:

the modification of cold curing acrylic cement to a porous cement by the addition of an aqueous gel as described in section 2.2 and having a composition as formulated in section 5.5 is a feasible way of obtaining a material which

- combines the advantages of in situ curing and "porous" attachment
- allows for bone ingrowth
- is biocompatible to a degree which is not lower and possibly even higher than is known of solid acrylic cement
- should be used in low-stress applications due to its mechanical properties
- may be used in human applications,without the expectation of greater risks than is known from the applications of solid acrylic cement.

In chapter 7,the experience with the animal studies is extrapolated to an indication of areas where the porous cement might be used clinically. Potential applications in reconstructive surgery, oral surgery and orthopaedic surgery are discussed. Preliminary results are given of a clinical trial which was initiated elsewhere using the porous cement for the augmentation of cranial deformities.

SAMENVATTING

Dit werk beschrijft in hoofdzaak de vervaardiging, ontwikkeling en beproeving van een mogelijk toepasbaar biomateriaal, namelijk koud hardend poreus polymethylmethacrylaat (PMMA). Onder de biomaterialen - dat zijn materialen die gebruikt worden voor vervanging, aanvulling of versteviging van ontbrekende of niet-functionerende delen van het menselijk lichaam - is PMMA een oude bekende.
In Hoofdstuk 1 (par. 1.2) wordt de geschiedenis van deze kunststof als biomateriaal beschreven en wordt een overzicht gegeven van vroegere en meer recente klinische toepassingen ervan.

Sinds enige tijd wordt veel aandacht besteed aan de mogelijkheid om door het gebruik van poreuze biomaterialen de hechting tussen het geïmplanteerde materiaal en de aangrenzende weefsels te verbeteren. Het is bekend dat zowel zacht als hard weefsel in staat is de poriën van zo'n materiaal binnen te groeien - als tenminste de poriediameter groot genoeg is - waardoor het implantaat aan zijn omgeving verankerd wordt.
In paragraaf 1.4 wordt het principe hiervan besproken aan de hand van voorbeelden van verschillende materialen en toepassingen. Tevens worden daar de beweegredenen gegeven om te komen tot de ontwikkeling van een poreus cement, waarin de voordelige mogelijkheden van porositeit en plastische verwerkbaarheid verenigd zouden zijn.

Het enige cement dat klinische toepassing vindt als implantatiemateriaal is massief PMMA-cement, ook wel acrylcement genoemd; het deed in de jaren vijftig intrede als materiaal voor heelkundige toepassingen. Hoofdstuk 2 bespreekt de voornaamste methoden voor de vervaardiging van poreus PMMA alsmede de, schaarse, pogingen die gedaan zijn om poreus PMMA cement te maken. In paragraaf 2.2 wordt de door ons gevolgde methode om poreus acrylcement te vervaardigen, beschreven. Deze bestaat uit het dispergeren van een waterige gel door het nog niet verharde mengsel van normaal botcement. Na het verharden ontstaat een twee-fasig materiaal waaruit de waterige fase door diffusie in de biologische omgeving kan verdwijnen onder achterlating van een netwerk van poriën in de kunststoffase. Deze poriën moeten het ingroeien van weefsel mogelijk maken.
Daartoe echter is het van belang de diameter van deze poriën alsmede de mate waarin zij onderling verbonden zijn en de diameter van die doorverbindingen te kunnen bepalen en te meten. In hoofdstuk 3 worden de methoden om dergelijke grootheden te meten besproken en van opmerkingen voorzien. De uitkomsten van deze metingen aan de poreuze struktuur van het cement en de invloed die bijvoorbeeld de gel viscositeit en de relatieve hoeveelheid toegevoegde gel hierop uitoefenen zijn vermeld in par. 3.4.

Voordat een biomateriaal toegepast kan worden, moet een verscheidenheid aan chemische en fysische eigenschappen ervan onderzocht worden om een inzicht te krijgen in de mogelijkheid van toxische of

irriterende invloeden die het materiaal zou kunnen uitoefenen op zijn biologische omgeving. Tevens moet daardoor vastgesteld worden of het materiaal kans maakt in de beoogde toepassingen bevredigend te functioneren.
De lange klinische ervaring die is opgedaan met massief acrylcement, heeft geleerd dat vooral twee eigenaardigheden van deze materialen aanleiding kunnen geven tot ongewenste verschijnselen, namelijk:
1. de hoge temperatuur piek die optreedt in het materiaal tijdens de sterk exotherme verhardingsreaktie.
2. de aanwezigheid in het materiaal, ook na verharding, van laag-molekulaire resten, met name van het monomeer methylmethacrylaat.

Deze aspecten van acrylcement worden besproken in hoofdstuk 4, par. 4.1. Aangezien het poreuze cement afgeleid is van massief cement, is het van groot belang het nieuw ontwikkelde materiaal op dezelfde aspecten te beproeven. De resultaten van dit laboratorium onderzoek staan in par. 4.2 en 4.3.

De mechanische eigenschappen van een biomateriaal bepalen in belangrijke mate de toepassingsmogelijkheden. Het is duidelijk dat het introduceren van porositeit een aantal mechanische eigenschappen van acrylcement niet ten goede komt. Er is dus de noodzaak om het nieuwe materiaal ook in dit opzicht te karakteriseren. In par. 4.4 wordt hiervan verslag gedaan aan de hand van de bepaling van druk-, trek-, buig- en slagsterkte, van de elasticiteitsmoduli, alsmede van de invloed die het poriën volume en de poriediameter hierop uitoefenen.

Uitgebreid dierexperimenteel onderzoek is een onmisbaar onderdeel van ontwikkelingswerk aan biomaterialen. Het moet bestaan uit histologisch onderzoek naar de reacties van harde en zachte weefsels op het aangrenzende implantaat en uit de bepaling van de mate waarin het biologische systeem wordt belast door bestanddelen van het materiaal. Aan de hand hiervan wordt de biocompatibiliteit vastgesteld. Vervolgens dienen biomechanische en op mogelijke toepassingen gerichte experimenten te worden uitgevoerd teneinde conclusies te kunnen trekken omtrent klinische bruikbaarheid en uiteindelijke gebruiksvoorwaarden.
Hoofdstuk 5 en 6 beschrijven de resultaten van een dergelijk vooronderzoek naar het gedrag van het poreuze cement.
In par. 5.1 wordt verslag gedaan van histologisch onderzoek na implantatie van het cement in het spongieuze bot van de varkensschedel. Ongunstige reakties van de weefsels als ontsteking, necrose en resorptie, alsook het gewenste aspect van botgroei in de poriën werden bepaald als funktie van poriegrootte, materiaal samenstelling en de tijd. Aan de hand hiervan kon een optimale samenstelling van het poreuze cement worden vastgesteld.
Experimenten met schapen en apen hadden het doel mogelijke toepassingen in de orthopaedische en plastische chirurgie te beproeven. De resultaten van dit onderzoek, dat uitgevoerd werd door anderen, worden samengevat in par. 5.2.
De concentratie aan monomeer methylmethacrylaat in het bloed van honden als gevolg van implantatie van het poreuze cement in de mergholte van het heupbeen, werd gemeten. Een vergelijk werd gemaakt met de situatie

die ontstond na het implanteren van massief cement.
De resultaten staan in par. 5.3.
Tenslotte is een poging gedaan massief en poreus cement te vergelijken voor wat betreft het opwekken van allergische (huid-) reakties.
Dit onderzoek werd verricht aan cavia's en wordt kort beschreven in par. 5.4.

In hoofdstuk 6 komen biomechanische experimenten ter sprake die informatie opleverden over de sterkte van het poreuze cement na ingroei van bot (par. 6.2) en over de kwaliteit van de verkregen fixatie tussen botweefsel en implantaat (par. 6.3).
De snelheid waarmee de sterkte van een botgedeelte waarin een kunstmatig aangebracht defect was gevuld met poreus cement, zich herstelde, werd gemeten (par. 6.4).

De resultaten van het onderzoek, zoals beschreven in de hoofdstukken 3 tot en met 6, leidden tot de volgende algemene conclusie:

de toevoeging van een waterige gel aan koud hardend acrylcement op een wijze zoals beschreven in par. 2.2 en met een samenstelling als beschreven in par. 5.5, is een bruikbare methode voor het verkrijgen van een poreus cement dat

- de voordelen van plastische verwerkbaarheid en hechting middels weefselingroei in één materiaal verenigt
- ingroei van bot toelaat
- in niet mindere mate en mogelijk zelfs in meerdere mate biocompatibel is dan massief botcement
- gezien de verminderde mechanische sterkte, toegepast moet worden in situaties waar lage belastingen te verwachten zijn
- bij klinische toepassingen geen grotere risico's op ongewenste bijwerkingen oplevert dan bekend zijn na gebruik van massief botcement.

In hoofdstuk 7 wordt de ervaring opgedaan bij de dierexperimenten benut voor het aangeven van mogelijke klinische toepassingen van het poreuze cement op het gebied van de orale, orthopaedische en plastische chirurgie. De eerste resultaten van een elders uitgevoerd klinisch experiment, waarbij het poreuze cement toegepast wordt voor schedelaugmentatie, worden daarbij kort besproken.

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STELLINGEN

I

Het dispergeren van een waterige Na - carboxymethylcellulose gel in het nog niet verharde mengsel van een botcement op basis van polymethylmethacrylaat levert een (latent) poreus cement op, waarvan de biocompatibiliteit die van het oorspronkelijke massieve cement tenminste evenaart.

Dit proefschrift, Hoofdstuk 5

II

Toepassing van poreuze implantatiematerialen waarin frequent poriën voorkomen met een diameter die te klein is voor ingroei van gevasculariseerd weefsel (< 20 µm), maar groot genoeg voor ingroei van niet gevasculariseerd weefsel (5 - 20 µm), dient vermeden te worden.

III

In poreuze materialen is de kans op het aanwezig zijn van een gemengde struktuur van "open" en "gesloten" porositeit zeer klein.

Dit proefschrift, 3.2.1.

IV

Het toevoegen van wateroplosbare, vaste deeltjes aan botcement, met het doel om in vivo een open porositeit te doen ontstaan, resulteert, ook bij gebruik van hoge percentages aan grote deeltjes, in een klein voor bot toegankelijk porievolume.

Dit proefschrift, 3.2.1.
Rijke et al. J.Biomed.Mater.Res.11:373,1977
Rijke et al. J.Bioeng. 2:333,1978

V

Tengevolge van de toegepaste analyse methode zijn de bevindingen van Petty, dat in de weefsels grenzend aan acrylaatcement-implantaten na korte tijd geen schadelijke concentraties aan methylmethacrylaat meer voorkomen, eerder indicatief voor de snelheid waarmee de verbinding in vivo wordt afgebroken dan voor de mate waarin deze uit het materiaal diffundeert.

Petty,W., J.Biomed.Mater.Res.14:427,1980

VI

Klinische toepassing van tandimplantaten anders dan binnen het kader van een experimenteel protocol is niet te rechtvaardigen zolang er niet méér inzicht bestaat in de voorwaarden voor een effektieve hechting van gingivaal weefsel aan het implantatiemateriaal.

VII

Het is vooralsnog niet voor de hand liggend te trachten om met één en hetzelfde materiaal aan de zeer verschillende voorwaarden die aan een tandimplantaat moeten worden gesteld, te voldoen.

VIII

Een ideale verbinding tussen bot en een implantaat zou zijn bereikt als het mogelijk is, zoals bij orthodontische behandelingen van natuurlijke elementen, het implantaat onder invloed van krachten met behoud van de fixatie van stand of plaats te doen veranderen.

IX

De reaktie-mechanismen die ten grondslag liggen aan de door redox-systemen geïnitieerde bulk-polymerisatie van methylmethacrylaat zijn onvoldoende begrepen.

X

Een gebitsbeschermer, zoals te dragen bij het beoefenen van diverse takken van sport, dient te bestaan uit een stijf, slagvast omhulsel dat gevoerd is met een zacht en slap materiaal en bij voorkeur zo gevormd is dat de frontelementen geheel worden ontlast.

Onderzoek uitgevoerd door Nijmeegse
tandheelkunde studenten, 1979 - 1981

XI

De grote moeilijkheden die studenten vaak ondervinden met het schrijven van een scriptie ter afsluiting van de studie hebben vooral te maken met de geringe aandacht die in de betreffende curricula is gevraagd voor het verwerven van de ertoe benodigde vaardigheden.

XII

Condens gerelateerde anignitie bij automobielen in koude jaargetijden, met als gevolg quasi - afasie van het locomotorisch centrum, kan eenvoudig en veelal autocuratief verholpen worden door siccatieve behandeling en eventueel curettage van de corpora ignitia na rotatie - extractie. Zonder therapie voor de, meestal causale, hypohydrogenhydrie van de accumulator is de kans op recidief echter groot.

7 januari, 1982